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Abstracts

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INV3
GETTING BELOW THE SURFACE OF THE GENETICS OF ANKYLOSING SPONDYLITIS
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AS is known to be highly familial (sibling recurrence risk ratio >52) and heritable (h²=90%). Whilst >80% of cases are HLA-B27 positive, only a minority of carriers of HLA-B27 develop AS (1-5%) and it is thought that multiple non-B27 genes are likely to interact to determine which B27-positive individuals develop the disease. In addition to HLA-B27, twelve loci have thus far been reported and confirmed to be associated with AS in white Europeans (ANTXR2, CARD9, ERAPI, IL12B, IL23, KIF1B, PTDGER4, RUNX3, TBKBP1, TNFR1, and chromosomes 2p15 and 21q22), and two loci have recently been reported in Han Chinese (HAPLN1-EDIL3, ANO6). These studies have involved moderate sample sizes and focused on common variants, and although these findings have been very informative about the aetioepithogenesis of AS, many genetic associations, including both common variants and rare variants with low population frequency, remain to be identified. In summary, these studies have scratched the genetic surface, and have illustrated how informative larger and more comprehensive studies could be.

It is clear from research in other diseases that international collaboration is required to make robust progress in genetic studies of common diseases. With this in mind, the International Genetics of Ankylosing Spondylitis Consortium (IGAS) was formed in 2003 with the goal of performing collaborative research in AS. Over the past 2 years, the consortium has performed a dense SNP genotyping study in 10,624 AS cases and 15,174 controls of European, Asian and South American ancestry, utilising available GWAS and deep sequencing data from different autoimmune diseases to provide a cost-effective platform for immunogenetic studies. Genetic data from RA, MS, Crohn’s, Crohn’s disease (CD) and ulcerative colitis (UC), along with other classical autoimmune diseases, were used in the chip design, making it a powerful platform for studies of pleiotropic genetic effects in these related diseases, and for fine-mapping of established loci and rare variant studies.

The IGAS consortium Immunochip study has identified at least a further 3 novel variants in HLA-C, IL12B and TRAF3IP2, and identified novel susceptibility loci for psoriatic arthritis (at 17q21 (SMARC1E); 18p11 (PTPN2); 11q23 (1.4×10^{-10}, TREH); and 19p13 (TYK2) (J. Bowes et al., Nature Genetics 2010; 42, 985-990) and smoking has been showing to delay the onset of inflammatory arthritis in psoriasis patients that are HLA-Cw06 negative (Eder L et al. Ann Rheum Dis 2012; 71: 219-224).

INV4
GENETICS OF PSORIATIC ARTHRITIS: SEARCHING FOR ARTHRITIS PREDISPOSING GENES IN PSORIASIS
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Although the etiology of psoriatic arthritis (PsA) is unknown, there is strong evidence to suggest that PsA is due to a complex interplay of genetic, environmental, and immunological factors. Among complex rheumatic diseases, PsA exhibits one of the strongest genetic contributions with relative risks among siblings ranging from 30 to 48 for PsA. However, despite the high heritability for PsA, there is a paucity of PsA specific genes. A perpetual problem in identifying arthritis predisposing genes is that PsA and psoriasis are inter-related disorders as most patients with PsA also have the skin pathology.

Genome-wide association scans (GWAS) has greatly advanced the genetics of psoriasis by focusing on SNP-based approaches in large case control datasets primarily among Caucasians of North European ancestry. To date over 30 psoriasis genes have reached genome wide significance. Many of the psoriasis genes can be integrated into a multi-tiered model that encompasses distinct signaling networks, comprising: skin barrier function (i.e., LCE3, DEFB4, GB2); the innate immune response (which involves NFKB and interferon signaling such as TNFAIP3, TNIP1, NFKBIA, REL, FBXL19, TYK2, NOS2); and the adaptive immune response (involving CD8+ T-cell and TH17-cell signaling such as HLA-C, IL12B, IL23R, IL23A, TRAF3IP2, ERAPI)). Published GWAS studies in PsA are limited A GWAS in UK PsA sample collection of 492 PsA cases and almost 6000 controls has confirmed association to previously identified PsA risk loci; HLA-C, IL12B, IL23R and TRAF3IP2 and to known PsV loci; IL23R, TNIP1, IL23A and RN1F14 (J. Bowes Ann Rheum Dis 2011; 70 (Suppl. 3): 209). They have also identified a number of novel potential susceptibility loci, which now require validation in additional data sets of PsA cases and controls. A more recent PsA GWAS that is presently being analyzed from Michigan group using 1526 PsA patients and 1500 controls from North America has identified TYK2 for the first time in PsA. This GWAS also noted that the signals at the HLA and IL12B differed between PsA and PsC. Thus presence of arthritis loci close to PsC loci or distinct arthritis-predisposing alleles at the PsC loci.

Fine-mapping of autoimmune susceptibility loci using immunochip by the UK PsA group in 929 PsA cases and 4537 healthy controls confirmed HLA-C, IL23R, TRAF3IP2, IL12B and identified novel susceptibility loci for psoriatic arthritis at 17q21 (SMARC1E); 18p11 (PTPN2); 11q23 (1.4×10^{-10}, TREH); and 19p13 (TYK2) (J. Bowes et al., Ann Rheum Dis 2012; 71 (Suppl. 3): 154).

When PsA has been compared to PsC certain genes do seem to be more frequently associated with PsA than psoriasis. However this appears to be exception rather than the rule as most genes identified in the skin pathology are expected to be identified in PsA. A recently published study from the University of Toronto PsA clinic in 712 PsA patients and 335 PsC patients noted the following alleles were found to be significantly associated with patients with PsA compared to patients with PsC in multivariate regression analysis: B*08 (OR 1.61, p=0.009), B*27 (OR 1.57, p=0.0001), B*38 (OR 1.65, p=0.026) and C*06 (OR 0.58, p=0.0002) (Eder L, Ann Rheum Dis 2012 Jan; 71(1): 50-5). Other HLA alleles have been recently been in case control for disease expression and progression and these will also be discussed at the presentation.

Replication in large cohorts, fine-mapping and resequencing efforts, together with functional studies of genetic variants identified, are now warranted to better understand susceptibility to and evolution of these diseases. Also gene–gene interaction and gene–environment interactions should be sought. Preliminary data of this kind are emerging. For instance a GWAS in psoriasis noted clear evidence of pairwise gene–gene interaction between a SNP in HLA-Cw*0602 and ERAPI (Strange A et al., Nature Genetics 2010; 42, 985-990) and smoking has been showing to delay the onset of inflammatory arthritis in psoriasis patients that are HLA-Cw06 negative (Eder L et al. Ann Rheum Dis 2012; 71: 219-224).

INV5
CELLULAR IMMUNOPATHOLOGY OF SPONDYLOARTHITIS
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Genome-wide association studies, experimental models and proof-of-concept clinical trials with novel biological agents have allowed us to better identify the molecular pathways involved in the pathophysiology of spondyloarthritides (SpA) over the last couple of years. These novel insights include alternative roles for HLA-B27 besides antigen presentation, the contribution of not only the TNF but also the IL-23/IL-17 pathway to SpA inflammation, and the contribution of Wnt and BMP signalling to osteoproliferation. However, it stills remains poorly understood which cells are operative in these pathways at the site of pathology in SpA. Whereas the contribution of lymphocytes is increasingly questioned, novel data point towards an important role of innate immune cells and stromal cells. The exact phenotype, function and hierarchy of these cells remains to be fully established. Using the TNF and IL-23/IL-17 axes as prototypical example, we will discuss the emerging role of polarized macrophage subsets, mast cells and innate lymphoid cells in human and experimental SpA. We will also discuss how the exact type of inflammation rather then the presence of inflammation as such may impact structural damage and, in particular, new bone formation. Finally, we will review recent data indicating primary alterations in stromal rather than inflammatory cells in SpA.
THE BIOLOGY OF HLA-B27
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HLA-B27 is one of the most intensely studied major histocompatibility complex (MHC) class I alleles, owing in large part to its central role in the pathogenesis of ankylosing spondylitis (AS) and related diseases. Elucidating the mechanism(s) by which HLA-B27 contributes to disease remains an important goal, and may provide novel insights that can be translated into better therapies or even disease prevention. In the last several years the recognition of aberrant properties of HLA-B27 including its tendency to misfold and form cell surface dimers, has spawned novel lines of investigation revealing unexpected links between this allele and activation of the IL-23/IL-17 axis. Together with genetic evidence implicating this axis, and the more recent identification of IL-23 responsive enthesal resident T cells in mice, a path from genotype to the unique spondyloarthritides (SpA) phenotype is beginning to emerge.

My presentation will briefly review both canonical and aberrant features of HLA-B27, including the influence of peptide cargo on MHC class I folding, misfolding, and stabilization in the context of recent evidence that ERAp1 and HLA-B27 interact in creating susceptibility to AS. Possible mechanistic links between aberrant features of HLA-B27 and the IL-23/IL-17 axis will be presented in the context of recent results from the transgenic rat model of SpA and how these data inform our understanding of disease mechanisms.

While it is likely that HLA-B27 serves as a pro-inflammatory stimulus in susceptible individuals and when expressed in rats, other features of the AS phenotype such as trabecular bone loss juxtaposed with aberrant bone formation are not completely explained by inflammation alone. The propensity of HLA-B27 to misfold, and when upregulated generate endoplasmic reticulum stress and activate the unfolded protein response (UPR), has additional implications for its role in disease. Since MHC class I molecules are expressed to varying degrees in many different cell types, including those involved in bone homeostasis, we have been studying whether HLA-B27 expression influences the development and function of osteoclasts (OCs) and osteoblasts. Preliminary results from our studies on OC development in transgenic rats reveal that HLA-B27 expression strongly promotes TNF-α induced OC formation not seen with overexpression of HLA-B7. By B27-expressing monocytes exposed to TNF-α it is both necessary and sufficient for increased OC formation. Interestingly, IFN-β production by these cells inhibits OC formation and partially counteracts the effect of IL-1α, as shown by substantially greater OC production when IFN-β is neutralized. Under the influence of TNF-α, HLA-B27 is upregulated, misfolded, and activates the UPR. While we have previously linked the UPR to IFN-β production, these results suggest that it may also lead to greater IL-1α expression. Taken together these data show that in this animal model, HLA-B27 expression can work downstream of TNF-α, altering cellular responses to this cytokine that may represent important modifiers of the SpA phenotype. Moreover, while the balance of IL-1α/IFN-β production under these in vitro conditions promotes OC formation, endogenous TLR ligands may alter this balance in vivo and could result in the net inhibition of osteoclastogenesis.

GUT INFLAMMATION IN SPONDYLOARTHITIS
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Extra-articular manifestations are affecting more than 1/3 of patients with spondyloarthritides, and steadily increase in importance over time. This particularly applies to the relation between gut and joint inflammation. Hence, microscopic gut inflammation, which occurs frequently in patients with SpA, is an important risk factor for clinical development of Crohn’s disease. Evidence has been presented that indicated that posterior gut inflammation equals to peripheral spondyloarthritides, highlighting its role across the entire disease spectrum. We proposed that the development of chronic bowel inflammation in these individuals occurs through a transition phase, in which inflammation becomes a chronic state. The transition model implies that different cell types are involved at different stages during disease progression, with stromal cells having an important role in chronicity. In addition, deficient regulatory feedback mechanisms or genetically determined alterations in antigen presentation, endoplasmic reticulum stress, autophagy or cytokine signaling might also favor a transition from self-limiting acute inflammation to chronic inflammation.

BIOLGICS IN SPONDYLOARTHRITIS: SUCCESS AND CHALLENGES
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The last 10-12 years have seen a rapid increase in our knowledge on treatment of spondyloarthritides with biologics. It started with the demonstration of a very good efficacy of TNF-blockers in ankylosing spondylitis (AS), first in small trials followed by large placebo-controlled treatment studies. Predictors for good response could be identified and a good efficacy was shown also in smaller trials. The introduction of biologics such as etanercept, infliximab and adalimumab resulted in a substantial proportion of patients reaching sustained remission or low disease activity. The last 10-12 years have seen a rapid increase in our knowledge on treatment of spondyloarthritides with biologics. It started with the demonstration of a very good efficacy of TNF-blockers in ankylosing spondylitis (AS), first in small trials followed by large placebo-controlled treatment studies. Predictors for good response could be identified and a good efficacy was shown also in smaller trials. The introduction of biologics such as etanercept, infliximab and adalimumab resulted in a substantial proportion of patients reaching sustained remission or low disease activity.
INV1

ADVANCES IN IMAGING OF SPONDYLOARTHITIS

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Conventional radiography can visualize bone erosion, sclerosis, joint space narrowing and new bone formation in sacroiliac joints and the spine, but is unfortunately not very sensitive in early disease. Diagnosis of ankylosing spondylitis (AS) is dependent on presence of bilateral moderate or unilateral severe radiographic sacroiliitis, as part of the modified New York criteria for AS. This has, until recently (see MRI below), delayed the diagnosis by 7-10 years. Furthermore, the modified Stoke’s ankylosing spondylitis spine score (mSASSS), which is the most sensitive radiographic method for monitoring structural damage in AS, is not very reproducible or sensitive to change, so improved methods for structural damage assessment are highly needed.

MRI has resulted in a major improvement in the evaluation and management of patients with SpA. Firstly, it permits earlier diagnosis, as MRI findings of active sacroiliitis form part of the recent ASAS criteria for axial spondyloarthritis. An additional diagnostic utility of structural findings in the sacroiliac joints has recently been documented. Secondly, MRI can provide objective evidence of currently active inflammation in patients with SpA. MRI is by far the best available method for detecting and monitoring inflammation in the spine and sacroiliac joints, and several validated assessment systems exist. Until the introduction of MRI, disease activity assessment was restricted to patient-reported outcomes. Furthermore, MRI can visualize structural damage (erosion, fat infiltration, syndesmophytes and ankylosis) in the sacroiliac joint and spine, but a clinical role of MRI for monitoring structural damage remains to be established.

Finally, certain MRI findings (inflammation at the vertebral corners) have predictive value with respect to subsequent development of radiographic syndesmophytes. However, clarification of the prognostic value of MRI in clinical practice requires further research.

Despite contrast-enhanced Doppler US has been reported to have a high negative predictive value for the detection of sacroiliitis, the role of US in assessment of sacroiliac involvement in AS and other types of axial SpA is minimal. In contrast, Ultrasonography is well-suited for assessment of peripheral joints and entheses.

INV2

CHALLENGES IN IMAGING - CLINICAL CORRELATIONS

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Spondyloarthritis (SpA) is a difficult disease to evaluate, particularly early in the disease course, because physical manifestations are often lacking and commonly used lab measures such as CRP are often insensitive. Magnetic resonance imaging (MRI) allows detection and quantification of active lesions which are highly responsive to therapy. These lesions manifest as increased signal on T1-weighted images of soft tissue, but this might be crucial for a better understanding of the pathogenesis of SpA. MRI has resulted in a major improvement in the evaluation and management of patients with SpA. MRI provides objective evidence of currently active inflammation in patients with SpA. MRI is by far the best available method for detecting and monitoring inflammation in the spine and sacroiliac joints, and several validated assessment systems exist. Until the introduction of MRI, disease activity assessment was restricted to patient-reported outcomes. Furthermore, MRI can visualize structural damage (erosion, fat infiltration, syndesmophytes and ankylosis) in the sacroiliac joint and spine, but a clinical role of MRI for monitoring structural damage remains to be established.

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INV13

MICROANATOMY OF ENTEHESITIS IN AS AND PsA

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The importance of enthesitis or inflammation at insertions has long been recognised in the spondyloarthropathies including ankylosing spondylitis (AS) and psoriatic arthritis (PsA). Enthesitis was considered as a focal lesion which was to some degree viewed independently from other manifestations including synovitis and osteitis. The importance of enthesitis for the pathogenesis of AS has been underestimated. Imaging and pathological studies have shown that the enthesitis lesion is not focal but is diffuse. The actual point of insertion of entheses to bone is invariably fibrocartilaginous in nature and is both avascular and aneuryscal. This is a functional adaptation to minimise stress and prevent inflammatory reactions at this site of particularly high force exertion.

Consequently in patients presenting with enthesitis imaging and microanatomical studies show evidence for inflammation in the adjacent bone, the adjacent tendon, the adjacent bursa with the actual insertion point in the bone being likened to the “eye of a hurricane”. Failure to recognise this important principle may lead investigators to the erroneous conclusion that enthesis is not primary since the inflammatory reaction may manifest in the immediately adjacent tissues. Since the original description of enthesopathy of spondyloarthritis a number of animal models including DBA1 model, mouse model, TNF transgenic models and more recently an Interleukin-23 over expression model and others are associated with an enthesopathy that manifests strictly at the entheses, but in later disease spreads to the adjacent synovium and bone. These animal models provide proof of principle of a primary enthesitis pathology in an animal model setting.

Of particular interest in humans character of the HLA-B27 gene is associated with the magnitude of peri enthesal osteitis in the heel and in the spine. However, the exact mechanisms of effect at the enthesis seem to be played out in bone at least in early disease. Several groups have reported inflammatory cell infiltration in the bone adjacent to insertions including macrophages, osteoclasts, T and B cells. Thus far no data pertaining to potential arthropoietic peptide repertoire have been derived from human enthesitis. The potential benefit for a better understanding of the underlying process is vast.

The differing micro anatomical structure and differing bio mechanics at different locations from the enthesis is associated with a differential distribution of erosions and new bone formation. Generally speaking erosions predominate in the early phases of enthesitis adjacent to fibre cartilage where there is extensive compression, but new bone formation tends to occur at the distal enthesis further away from the fibrocartilage at sites where there is predominant tension. It remains unclear as to the molecular mechanisms accounting for new bone formation at insertions following inflammation but in animal models there is good evidence for BMP pathway signalling as key orchestrators.

Sub clinical enthesopathy is common in patients with psoriasis and in patients with inflammatory bowel disease and patients with anterior uveitis- none of whom have clinical arthritis. Given the difficulty in accessing tissue from the enthesis the clinical pathological significance of these changes remains to be determined. Whether such changes represent inflammation could be key to understanding the pre-clinical phase of enthesal driven inflammation. Thus far, specific genes related to an enthesitis driven pathology in man have not been clearly defined.

High resolution imaging studies have also shown an important emergent role for the enthesis and adjacent ligament or tendon in the pathogenesis of osteoarthritis (OA). This is especially relevant from the clinical perspective of as differentiation between psoriatic and inflammatory osteoarthritis particularly in the small joints of the hands can be difficult. Several groups have now shown an important role for the enthesis in experimental and clinical OA. With respect to therapy the potential of TNF agents have been proved exquisite in their ability to suppress enthesitis and osteitis as determined by imaging. Thus, far there is a paucity of data on other emerging targets used to treat polyarthritis related pathology including data from therapies that suppress the IL-17/IL-23 axis.
INV14

BONE HOMEOSTASIS

Goldring S.R.

In addition to its role in providing a system for regulation of mineral ion homeosta-sis and mechanical and structural support, the skeletal system is uniquely adapted to additional functions that include a role in energy metabolism and the maintenance of a "niche" for stem cells for tissue regeneration and repair and support of the bone marrow hematopoietic system. These diverse functions are dependent in part on the integrated activities of a network of cell populations that form a so-called bone multicellular unit (BMU). The BMU consists of myoid lineage osteoclasts, which are uniquely adapted to resorbing the mineralized bone matrix, osteoblasts that synthesize the bone matrix and osteocytes that are embedded in the bone ma-trix and play an essential role in mechanotransduction and skeletal remodeling. The differentiation and function of these cell populations are regulated by growth factors, cytokines, soluble small molecule mediators and cell surface ligands and receptors that orchestrate and integrate the activities of these cells in response to local environmental factors and systemic endocrine hormones. In inflammatory joint diseases such as ankylosing spondylitis, psoriatic arthritis, rheumatoid arthri-tis (RA) and systemic lupus erythematosus, the bone microenvironment is invaded by cells that disrupt the physiological balance in bone resorption and formation resulting in profound alterations in the structural and functional properties of the peri-articular bone. Several lines of evidence have established that osteoclasts, the cells that are essential for physiological bone remodeling, mediate the pathological bone resorption associated with the various forms of inflammatory arthritis. The synovium from RA and related forms of destructive inflammatory arthritis contains osteoclast precursors, and importantly the synovial tissue is a source of multiple potent osteoclast-inducing cytokines and growth factors, including receptor activa-tor of NF-κB ligand (RANKL), the master regulator of osteoclastogenesis without which there is an inability to form osteoclasts. RANKL is produced by multiple cell types, including synovial fibroblasts and T cells within the synovium, as well as osteocytes, hypertrophic chondrocytes and osteoblast lineage stromal cells. An addi-tional distinguishing feature of the inflammatory arthropathies is the differential patterns of bone formation and repair observed in RA and the spondyloarthropathies (SpAs). In RA, there is a virtual absence of peri-arterial bone formation and repair, whereas in the SpAs there is evidence of focal regions of enhanced bone formation at sites of articular and spinal inflammation. Recent insights into the regulation of bone formation have come from the dissection of the role of the wingless (Wnt)-signaling pathway in controlling osteoblast differentiation and bone formation. Of particular interest has been the role played by inhibitors of this pathway that include sclerostin and the family of dickkopf (DKK) proteins, both of which are produced by synovial fibroblasts. Under physiological conditions, sclerostin and local Wnt signaling are required for the osteogenic response to mechanical loading and play a critical role in bone adaptation and remodeling. The effects of the Wnt ligands on osteoblasts and bone formation are mediated via the canonical Wnt pathway that interacts with a receptor complex consisting of the LRP5/LRP6 and frizzled-related proteins. Ligation of this receptor complex results in downstream signaling that leads to translocation of β-catenin to the nucleus where it enhances osteoblast dif-ferentiation and activity and down-regulates OPG (the inhibitor of RANKL). While involvement of the Wnt proteins consist of a large family with diverse functions. In osteoclast lineage cells, the canonical pathway is activated by the Wnt agonist Wnt3a and inhibited by Wnt5a. There is an additional noncanonical Wnt pathway that mediates effects via a single transmembrane receptor Rox1/2. With this receptor, the roles of the Wnt ligands are reversed, and Wnt3a functions as an inhibitor and Wnt5a as an agonist for bone resorption. Of interest, although the inflamed synovium contains abundant osteoclast precursors that exist in an environmental milieu that is rich is osteoclas-togenic cytokines and growth factors, cells with definitive features of osteoclasts are almost entirely restricted to the bone surface. This suggests that local factors in the immediate bone microenvironment, including components of the bone sub-strate, provide signals that are essential for terminal osteoclast differentiation and activation. In recent studies we have utilized an in vitro osteoclast differentiation model to characterize the genes and gene products that are regulated by interaction of osteoclasts and their precursors with an authentic bone substrate. Our results pro-vide evidence that in addition to soluble mediators and direct cell-cell interactions, the bone substrate also contributes to the regulation of osteoclast differentiation and activation, and importantly reveals additional targets for potential control of pathological bone remodeling in inflammatory arthritis.

INV16

THE EPIDEMIOLOGY OF SPONDYLOARTHRITIS

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Chronic low back pain is a leading cause of disability and lost productivity. Re-cent data from the United States (U.S.) National Health and Nutrition Examination Survey (NHANES) have documented that the prevalence of chronic back pain has risen dramatically from 5% in the 1970’s to 19.3% in 2009-2010. There are various criteria for inflammatory back pain (IBP) however NHANES es-timates that 6.9% of Americans had chronic IBP, most common in younger adults. Axial spondyloarthritis (AxSpA) is a recently defined concept encompassing ankylosing spondylitis (AS) as well other types of SpA with an axial component. As few criteria are being developed and validated, knowledge of the epidemiology of spondyloarthritis (SpA) has advanced significantly. The prevalence of AxSpA in the U.S., as defined by ESSG Criteria, is estimated at 1.4% in the 2009-2010 NHANES study, with women affected slightly more commonly than men and non Hispanic blacks least commonly affected.

In NHANES 2009-2010 28/5103 (0.54%) individuals carried a diagnosis of AS. These data are strikingly similar to the prevalence of moderate-to-severe sacroiliitis seen in the U.S. in NHANES 1 (1971-1975) (0.52%), which is in turn similar to other population based cross-sectional data reported from Germany and China. Older estimates from the U.S. suggesting lower frequencies of AS were neither population nor criteria-based.

The frequency of AS around the world parallels the frequency of HLA-B27, lowest in Africa (where cases of SpA tend to not possess B27) and Japan and highest in in circumpolar groups (Sami, Inuits), where HLA-B27 is found in one third of the population. The nationally-representative frequency of HLA-B27 in NHANES 2009 in the U.S. is 6.1%, lowest in blacks (1.1%) and highest in whites (7.5%). Of particular note was the finding of significantly lower HLA-B27 prevalence es-timates for the older as opposed to younger U.S. adults (3.6% for those 50-69 years of age vs. 7.3% for those 20-49 years, respectively). Although the reason for this cannot be determined from this cross-sectional survey, one interpretation is that HLA-B27 positive individuals die prematurely. These data must be further repli-cated in other groups.

The transient nature of reactive arthritis (ReA) in many patients makes determina-tion of it prevalence difficult, although recent data on the incidence of ReA vary from 9-27/100,000/year, with enteric causes more frequent that urogenital causes. Psoriatic arthritis occurs in 1.2-3.5% of population, most common in northern Europe and least common in Asia. Psoriatic arthritis (PsA) occurs in 6% to 39% of psoriasis patients, depending on the case series; the true prevalence is probably in the 10-25% range.

Worldwide, the incidence rates for IBD vary from 0.5 to 24.5 per 100 000 person-years. The prevalence of enteropatric arthritis/spondylitis in those with IBD like-wise varies widely, depending on how and who did the ascertainment, ranging from 17-62%, with peripheral arthritis generally more common than axial involvement. Overall, SpA occurs at higher frequency than most other rheumatic diseases, in-cluding rheumatoid arthritis. What this means as far as an unmet need as far as treatment burden an utilization is concerned is one of the challenges facing modern rheumatology.

INV17

EARLY COHORTS IN Spondyloarthritis

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Cohort studies provide important information about clinical manifestations, the natural course of disease, outcome, and predictors of outcome. While in the past most often cohorts in longstanding ankylosing spondylitis (AS) were studied, more recently focus was put on early AS, in particular on early non-radiographic axial SpA (nr-axSpA). The German Spondyloarthritis Inception cohort (GESPIC) was one of the first invented inception cohorts aiming to study prospectively the disease-course, outcome and predictors of outcome in AS and in non-radiographic axial SpA (nr-axSpA). AS patients in this observational cohort had a mean duration since diagnosis of only 2.8 years, and a duration of symptoms of only 5.2 years on average, reflecting truly early AS. Of note, clinical manifestations were similar between AS and nr-axial SpA patients. HLA-B27 has been known to be associated with an earlier age at onset in AS. This was confirmed in GESPIC for AS and was demonstrated for the first time also in nr-axSpA patients, thereby underlin-ing the concept of axial SpA being a disease continuum. In another cohort from France referred to as DESIR which is a large prospective cohort of 654 patients with inflammatory back pain of no more 3 years and fulfillment of at least one set of SpA classification criteria, the association of HLA-B27 with age at onset was confirmed (2). The role of HLA-B27 for disease severity in axial SpA, however,
DENSE GENOTYPING OF CANDIDATE GENES IDENTIFIES 16 NEW SUSCEPTIBILITY LOCI IN ANKYLOSING Spondylitis

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Introduction/Aim: Ankylosing spondylitis (AS) is a highly heritable inflammatory arthritis common in both Asian and European populations. Thus far genes identified include the HLA-B27 allele, and non-MHC loci identified in European populations. In this study we aimed to better characterize the genetic architecture of AS and to fine-map known susceptibility loci.

Materials and Methods: We successfully genotyped 129,030 polymorphic SNPs in 10,624 AS affected and 15,174 healthy individuals of European and Asian descent using the Illumina Immunochip microarray, which was designed for immunogenetic studies.

Results: In this study we identified 16 new AS risk loci reaching genome-wide significance (p<5x10^{-8}), bringing the number of known non-MHC loci to 27. We found multiple independent association signals in 8 of these loci, caused by both common and low frequency variants, suggesting that multiple genetic variants within a gene can affect disease susceptibility. A second MHC association with the classical HLA-A*0201 allele was observed in both HLA-B*27 positive and negative disease (OR=1.2, p=5.6x10^{-10}). European and Asian specific signals were observed in IL23R and PTPN22.

Discussion: This study has replicated all attempted genome-wide significant loci reported in European populations and identified 16 novel susceptibility loci. Identified loci implicate microbial sensing (NOD2, NLRX2, J, SLE,3, IECOSIG), intra-cellular antigenic peptide handling (ERAP1, ERAP2, LNPEP, NPEPPS) and CD8+ T cells (EOMES and IL7R) pathways as important in AS etiology as well as increase the number of susceptibility genes in the TH17 pathway (TYK2 and IL6R).

Conclusion: This increased characterization of the genetic architecture of AS aids greatly in explaining the currently poorly understood high observed heritability and familiarity in AS. This data also guides functional studies towards uncovering how these genes cause disease and in the development of new therapeutics.
Conclusions: This study identifies robust association with three loci housing four aminopeptidases, ERAP1, ERAP2, LNPEP, and NPEPPS. This implicates peptide handling as a major mechanism in the aetiology of both HLA-B27 positive and negative AS.

Results: HLA-B27 dimers were preferentially detected in association with the cellular degradation machinery. Uprolification of the UPR suppressed HLA-B27 dimer formation, whilst down regulation prevented their formation. ERAD markers correlated with dimer levels in AS patients.

Discussion: The UPR induced degradation machinery exhibits remarkable specificity in targeting HLA-B27 dimers. Though ER stress induced by HLA-B27 misfolding has been described to be pathogenic, it is possible that the UPR could be used therapeutically to alleviate the toxicity associated with aggregated protein. The degradation pathway for HLA-B27 dimers described here presents a potential novel therapeutic target for the modulation of HLA-B27 associated inflammatory disease.

Conclusion: HLA-B27 dimers can be specifically targeted for UPR induced degradation.

ENDOPLASMIC RETICULUM AMINOPEPTIDASE-1 (ERAP1) PLAYS A CRITICAL ROLE IN PEPTIDE BINDING AND ANTIGEN PRESENTATION BY HLA-B27

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Introduction: Recent studies have shown that genetic variation within ERAP1 is strongly associated with Ankylosing Spondylitis (AS) in HLA-B27 (B27) positive individuals. Within the endoplasmatic reticulum (ER), ERAP1 is involved in the trimming of peptides to the optimal length for their presentation by major histocompatibility complex (MHC) class 1 proteins, such as B27. Here, we investigated the role of ERAP1 in AS pathogenesis by studying the effect of ERAP1 silencing on the B27 peptide repertoire and the presentation of a HIV gag B27 epitope, KR-WIILGLNK (KK10), to cytotoxic T lymphocyte (CTL).

Materials and Methods: 1) Stable ERAP1 silencing: ERAP1-siRNA plasmid was constructed and cloned into a lentiviral plasmid. ERAP1-siRNA lentivirus was then produced to stably silence the expression of ERAP1 on C1R.B27 and HeLa B27 cells.

2) B27 peptide preparation and mass spectrometry: B27 expressing cells ± ERAP1 were labelled separately using SILAC technique (stable isotope labelling by amino acids in cell culture), then mixed before lysis and immuno-purification using W632 for MHC class I or ME1 for B27 in combination with Protein G Dynabeads/ sephrose. The peptides bound to B27 were eluted and analyzed by MS.

3) HIV-gag B27 CTL activation assay: Cells were infected with recombinant HIV gag vaccinia and co-cultured with HIV-gag B27 epitope specific cytotoxic T lymphocyte (CTL) overnight. IFN-gamma ELISpot were used to measure the number of CTLs activated.

Results: 1) Using an ERAP1-siRNA lentivirus, more than 90% of stable ERAP1 silencing was achieved in HeLa.B27 cells, approximately 80% in C1R.B27.

2) The percentage of long HLA-B27 peptides, 10mer-11mer, was increased when ERAP1 was silenced in HeLa.B27 cells. Similarly, in ERAP1 silenced C1R.B27 cells, the proportion of 11mer-13mer peptides were increased.

3) ERAP1 silenced C1R.B27 presents gag-B27 epitopes differentially to CTLs.

Conclusions: ERAP1 is a key ER aminopeptidase in the MHC class I pathway, whose silencing reshapes the B27 peptide repertoire, resulting in longer peptides. Our study suggests that abnormal ERAP1 forms may change the repertoire of peptides bound to B27 and affect cells’ ability to present B27 epitopes to CTL for immune surveillance in a biologically meaningful way.

IL-23 INDUCES SPONDYLOARTHRITIS BY ACTING ON RORGT+, CD3+, CD4+CD8+ DOUBLE NEGATIVE ENTHESAL RESIDENT CELLS

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Introduction/Aim: Spondyloarthritis is characterised by inflammation and bony pathology at the enthesal insertion of tendons to bone. Recent investigations have converged upon interleukin(IL)-23, demonstrating firstly that genetic variants in its receptor are associated with disease and secondly that HLA-B27, which is present in 90% of patients with ankylosing spondylitis, has a tendency to misfold and form cell surface homodimers resulting, respectively, in production of IL-23...
and stimulation of IL-23R+ cells. However why dysregulation of IL-23 should result in inflammation primarily at the enthesis has remained deeply enigmatic.

Materials and Methods: We used GFP reporter mice to investigate the tissue distribution of IL-23R+ cells in the enthesis, and examined the effect of IL-23 on this tissue using RNA expression vectors.

Results: Entheses contain an IL-23R+ T lymphocyte, negative for both CD4 and CD8, which allows this tissue to respond to IL-23 in vitro. Multiphoton microscopy confirms an extremely precise entheseal cellular localisation. IL-23 expression in mice is sufficient by itself to induce hallmark features of spondyloarthropathy with severe inflammation developing rapidly and specifically at the enthesis without initial articular pathology. Entheseal bone erosion, new bone formation and periostitis are likewise present. IL-23+ CD4+ CD8- T cells are also located in the aortic root and valve and IL-23 expression induces aortitis.

Discussion: The highly restricted anatomical distribution of IL-23+ cells explains both the tissue localisation of disease to the enthesis and the known genetic associations. The importance of the tissue resident cells is emphasised by the ability of IL-23 to drive enthesis despite depletion of CD4+ Th17 cells.

Conclusions: Neutralisation of IL-23 represents an excellent therapeutic strategy in spondyloarthropathy since it will inhibit a potent downstream action of known genetic factors, and do so directly at the site of pathology.

O6
THE EFFECT OF ANTI-TUMOR NECROSIS FACTOR THERAPY WITH GOLIMUMAB ON RADIOGRAPHIC PROGRESSION IN DEFINITE ANKYLOSING SPONDYLITIS: 4-YEAR RESULTS

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Background/Purpose: Three clinical trials in which structural spinal changes in patients with ankylosing spondylitis (AS) treated with tumor necrosis factor (TNF) antagonists over 2 years (yrs) were assessed in comparison to a historical cohort have indicated that such therapy may not alter radiographic progression as quantified by the modified Stokes Ankylosing Spondylitis Score (mSASSS). Longer-term data are scarce. The purpose of this study is to assess the effects of the anti-TNF agent golimumab (GLM) on radiographic progression in patients (pts) with AS through 4 yrs of treatment.

Methods: Pts (n=356) were randomly assigned (1:1:1:1) to subcutaneous injections of PBO, GLM 50mg, or GLM 100mg q4wks (wks). At wk16, pts in the PBO or 50mg groups with ≥20% improvement in both total back pain and morning stiffness entered early escape (EE) to GLM 50 or 100mg, respectively. At wk24, pts still receiving PBO crossed over (CO) to GLM 50mg. Lateral view radiographs of the cervical and lumbar spine were performed at baseline, wk104 and wk208. Radiographs were read by 2 independent, central, trained readers using mSASSS methodology (0=normal; 1=erosion, sclerosis, or squaring; 2=syndesmophyte; 3=bridging syndesmophyte). The mSASSS ranges from 0-72.

Results: Among all randomized pts, median time since first AS symptoms was 11.0 yrs. Treatment groups were comparable with regard to age, gender, BASDAI, BASFI, BASME, CRP, mSASSS, and baseline syndesmophytes. Overall mean changes in mSASSS at wk104 and wk208, with no obvious treatment group differences, and 3.6 at wk208, with numerically larger changes in the GLM 100mg group (Table). Due to wide distribution of change values, the numerical differences in mean change for the 100mg group or for the 19 radiographically evaluable pts who still received PBO crossed over (CO) to GLM 50mg. At wk24, 23.1% and 35.1% of pts had a definitive change (>2 points) in mSASSS.

Conclusions: Changes in mSASSS from baseline to wk104 and wk208 indicated that anti-TNF treatment with GLM does not inhibit radiographic progression in the spine of pts with AS.

O7
ELEVATED LEVELS OF WNT3A AND LOW LEVELS OF DICK-KOPF-1 IN SERUM ARE ASSOCIATED WITH SYNDROME FORMATION IN ANKYLOSING SPONDYLITIS

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Introduction and Aims: Ankylosing spondylitis (AS) is associated with both pathologic formation of new bone and enhanced bone resorption. The objectives of this study were to assess a panel of biomarkers reflecting bone formation and to determine their relationship with syndesmocyte formation, bone mineral density (BMD) and disease activity in AS.

Methods: Levels of biomarkers were measured with sandwich enzyme-linked immunosorbent assays (ELISA) in patient sera and compared with levels of healthy blood donor controls. The biomarkers studied were: Wingless proteins (Wnt3a, Wnt5a), Dickkopf-1 (Dkk-1), sclerostin, soluble receptor activator of nuclear factors-kb ligand (sRANKL) and osteoprotegerin (OPG) BASDAI, ASDAS and CRP were chosen as disease activity parameters. Hip mobility was assessed for calculation of BASMI. Lateral spine radiographs were scored for syndesmophyte formation (mSASSS). BMD was measured with dual energy x-ray absorptiometry (DXA).

Results: 204 AS patients (NW-criteria) (57% men) with a mean age of 50±13 years and disease duration 15±11 years and 80 age and sex matched controls were included. The AS patients had significantly higher levels of Wnt3a (3.7±0.6 vs. 2.8±0.4 pmol/mL; p<0.001) and lower levels of sclerostin (35.3±21.54 vs. 33.3±15.96 pmol/L; p<0.014) compared with the controls. Wnt3a was positively correlated with BASMI (r=0.219; p=0.002) and mSASSS (r=0.196; p=0.005) but negatively correlated with BMD femoral neck (r=-0.160; p=0.023). High CRP was significantly correlated with lower levels of sclerostin (r=-0.208; p=0.003) and Dkk-1 (r=-0.140; p=0.045). Femoral neck BMD was significantly correlated with high CRP (r=0.160; p=0.023) and lower levels of Wnt3a (r=-0.208; p=0.003) and mSASSS (B=0.010; p=0.003) were independently associated with low Z-score for BMD femoral neck (R²=0.091).

Conclusions: Wnt3a could be a marker for syndesmophyte formation in AS.

O8
BIOMECHANICAL STRESS AS A TRIGGER FOR ENTHESITIS AND NEW BONE FORMATION IN Spondylarthritides

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Spondylarthritides (SpA) are characterized by axial and peripheral arthritis and enthesitis, leading to new bone formation and eventual to ankylosis. The aim of this study was to investigate the development of enthesitis in TNFα436 mice, an established model for SpA, and to study events leading to new bone formation. TNFα436 mice are characterized by an enhanced TNF mRNA stability, which leads to accelerated development of peripheral arthritis and Crohn’s-like ileitis. One of the striking features of this model is the early appearance of enthesitis of the Achilles tendon.

TNFα436 mice which had not yet developed signs of inflammation were subjected to tail suspension, a biomechanical unloading procedure, thereby prohibiting weight bearing on hind paws for 14 days. Almost no inflammation of the Achilles tendon occurred in unloaded animals compared to weight bearing controls. By contrast, weight bearing front paws exhibited severe inflammation. Within 15 minutes after reloading, Western blotting demonstrated up regulation of phosphorylated Erk MAP kinase (ppErk) and actin filament (F-actin) levels and suppression of actin filament (F-actin) levels and suppression of collagen type I (Coll I).

Table: Baseline and change from baseline in mSASSS

<table>
<thead>
<tr>
<th>PBO</th>
<th>GLM 50mg</th>
<th>GLM 100mg</th>
<th>All GLM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (n=60)</td>
<td>16.1 (18.7)</td>
<td>11.7 (16.4)</td>
<td>13.5 (18.9)</td>
</tr>
<tr>
<td>Median</td>
<td>7.9</td>
<td>3.1</td>
<td>3.5</td>
</tr>
<tr>
<td>Wk104</td>
<td>1.6 (4.6)</td>
<td>0.9 (2.7)</td>
<td>0.9 (3.9)</td>
</tr>
<tr>
<td>Median change</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>% pts with change &gt;2</td>
<td>17 (25.8%)</td>
<td>22 (19.8%)</td>
<td>30 (24.6%)</td>
</tr>
<tr>
<td>Wk208</td>
<td>3.2 (8.6)</td>
<td>2.4 (6.6)</td>
<td>4.9 (10.6)</td>
</tr>
<tr>
<td>Median change</td>
<td>0.5</td>
<td>0.0</td>
<td>1.1</td>
</tr>
<tr>
<td>% pts with change &gt;2</td>
<td>22 (33.3%)</td>
<td>34 (30.6%)</td>
<td>49 (40.2%)</td>
</tr>
</tbody>
</table>

p≤0.05

1Includes pts who died (n=19) and did not (n=92) meet the early escape criteria at wk16.

2Includes pts who did (n=25) and did not (n=97) meet the early escape criteria at wk16.
kinase in Achilles tendon cell lysates of tail suspended TNF\textsuperscript{ENR} mice. Treatment of TNF\textsuperscript{ENR} mice with small molecular Erk or p38 inhibitors markedly reduced the extent of Achilles tendon enthesitis. In addition, cyclic stretch was performed on fibroblasts from TNF\textsuperscript{ENR} and control mice in a bioreactor, which demonstrated a differential chemokine production in supernatant from stretched TNF\textsuperscript{ENR} fibroblasts versus controls. This in turn resulted in enhanced migration of lymphocytes towards conditioned medium from stretched TNF\textsuperscript{ENR} fibroblasts. As TNF\textsuperscript{ENR} mice do not develop new bone formation, this feature was studied in the collagen antibody-induced arthritis (CAIA) model, in which a collagen type II antibody cocktail provokes a rapidly destructive peripheral arthritis that regresses within days. After resolution of arthritis, half of the group of mice were suspended by the tail. After four weeks of tail suspension, osteophyte growth was studied in both groups by micro- and nano-CT, and histology. Osteophytes appeared markedly larger in non-tail suspended mice.

Conclusion: These findings substantiate the hypothesis that biomechanical stress can activate pro-inflammatory signaling pathways, which in a genetically predisposed host may lead to enthesitis. Furthermore, mechanical stress may enhance new bone formation.

O9

STRUCTURAL PROGRESSION OF ANKYLOSING SPONDYLITIS ASSOCIATED WITH ELEVATION IN TWO NOVEL, INFLAMMATORY BIOMARKERS: MATRIX METALLOPROTEINASE AND CATHEPSIN-DERIVED CRP

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Background: Current inflammatory biomarkers, such as CRP, have insufficient sensitivity and specificity to be broadly accepted for diagnosis and prognosis of AS. We hypothesized, that quantification of inflammation markers derived from the affected tissue might have improved clinical utility compared to the systemic markers. We developed two novel biomarker assays detecting MMP and cathepsin-derived CRP (MMP-CAT and CAT-CRP) and aimed to determine their diagnostic utility and association with radiological progression.

Methods: Serum samples (n=124) from AS patients, mean disease duration (SD) 18.0 (11.4) years were assessed. Within this cohort, samples from 16 AS patients with structural progression over two years and 29 without were selected for prognostic evaluation (sub-cohort 1A). A progressor was defined as having a baseline mSASSS of ≥5 units and progression of ≥5 units plus ≥1 new syndesmophyte over two years. Non-progressors were defined as disease duration at baseline of >10 years, baseline mSASSS <5 units, and no change in mSASSS over 2 years Sub-cohort 1B comprised samples from 53 AS patients pre- and post- anti-TNF treatment. We also included samples (n=29) from healthy controls.

Results: Mean age was 40 years (SD ±11), mean BASDAI was 6.1 (SD ±1.9), and 59% were male. Syndesmophytes were present in 31 of the 53 (58%) patients. Patients with syndesmophytes had significantly higher levels of PINP (median Z-score: 0.85 vs. -0.09, p=0.005) and sCTX (median Z-score: 0.33 vs. -0.42, p=0.033) compared to patients without syndesmophytes. No significant differences were found in BALP (median Z-score: 1.58 vs. 0.89, p=0.144) and BASDAI (mean: 6.1 vs. 6.0, p=0.813) between patients with and without syndesmophytes.

Conclusion: This cross-sectional univariate analysis in AS patients with active disease shows that markers of both bone formation (PINP) and bone resorption (sCTX) are significantly higher in patients with syndesmophytes compared to patients without syndesmophytes. Longitudinal studies with multivariate analyses are needed to investigate whether BTM can serve as potential biomarkers for radiographic damage in AS.

O10

SYNDESMOHYTES ARE ASSOCIATED WITH HIGHER BONE TURNOVER IN ANKYLOSING SPONDYLITIS PATIENTS WITH ACTIVE DISEASE

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Introduction: Our aim was to investigate the relation between the presence of syndesmophytes and bone turnover markers (BTM) in ankylosing spondylitis (AS) patients with active disease.

Methods: Fifty-three consecutive outpatients with AS (fulfilling the modified New York criteria) and active disease (BASDAI >4 and/or based on expert opinion) were included. Patients with recent fractures, use of bisphosphonates, and/or inflammatory bowel disease were excluded. The lateral view of cervical and lumbar spine radiographs were scored for the presence of syndesmophytes at the anterior corners of the vertebrae by two independent observers. In case of discrepancy between the observers, consensus was reached afterwards. Markers of bone formation pro-collagen type 1 N-terminal peptide (PINP) and bone-specific alkaline phosphatase (BALP), and marker of bone resorption serum collagen-telopeptide (sCTX) were measured. Z-scores of BTM were calculated using matched 10-years-cohorts of a Dutch reference group to correct for the normal influence that age and gender have on bone turnover.

Results: Mean age was 40 years (SDs ±11), mean duration of symptoms was 15 years (SDs ±11), mean BASDAI was 6.1 (SDs ±1.9), and 59% were male. Syndesmophytes were present in 31 of the 53 (58%) patients. Patients with syndesmophytes had significantly higher levels of PINP (median Z-score: 0.85 vs. -0.09, p=0.005) and sCTX (median Z-score: 0.33 vs. -0.42, p=0.033) compared to patients without syndesmophytes. No significant differences were found in BALP (median Z-score: 1.58 vs. 0.89, p=0.144) and BASDAI (mean: 6.1 vs. 6.0, p=0.813) between patients with and without syndesmophytes.
SO1

EXPRESSION OF HLA-B27 CAUSES LOSS OF MIGRATORY DENDRITIC CELLS IN A RAT MODEL OF SPONDYLOARTHROPATHY

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Introduction: A genetic predisposing factor shared by the spondyloarthritides is the MHC class I gene HLA-B27. Rats transgenic for human HLA-B27 and B27-microglobulin (B27-TG rats) spontaneously develop colitis and peripheral inflammation, thus providing a model of SpA. Because this inflammation requires CD4+ T lymphocytes and involves intestinal pathology, we aimed to discover whether the dendritic cells (DCs) that migrate from the intestine and control CD4+ T cell differentiation were aberrant in B27-TG animals.

Methods: Migrating intestinal lymph DCs were collected by thoracic duct cannulation from B27-TG and control rats. The phenotype and response to PWM (possibly due to the unique N-terminal flanking and P1 residues) of these, and of mesenteric lymph node DCs, were assessed by flow cytometry. Also, the functions of DCs differentiated from bone marrow precursors in vitro were assessed.

Results: Strikingly, B27-TG animals lack one subset of L-DCs, the MHCII CD172alo DCs, in both the lymph and in the mesenteric lymph nodes. In addition, the remaining B27-TG L-DCs express more CD25, indicating increased activation. Furthermore, in vitro culture of DCs from bone marrow precursors with Flt3L revealed reduced survival of B27-TG DCs, suggesting a systemic defect in B27-TG DC differentiation. In spite of the reduced viability of B27-TG BMDCs, they induced enhanced IL-17 production from naïve CD4+ T cells in vitro.

Discussion: The CD172alo DC subset has been implicated in the induction and maintenance of intestinal tolerance, and thus lack of this subset could lead to breakdown in tolerance and to systemic disease. In addition, the enhanced IL-17 production from CD4+ T cells stimulated by the surviving B27-TG BMDCs could contribute to inflammation in these animals.

Conclusion: We describe two different DC-dependent mechanisms by which HLA-B27 may contribute to inflammatory disease in B27-TG rats.

SO2

FUNCTIONAL INTERACTION BETWEEN THE ANKYLOSING SPONDYLITIS ASSOCIATED ERAP1 POLYMORPHISM AND HLA-B27 IN VIVO

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*The contribution of N. García-Medel and A. Sanz-Bravo to this work was equal.

Introduction/Aim/Materials and Methods: The association of ERAP1 with ankylosing spondylitis (AS) among HLA-B27-positive individuals suggests that ERAP1 polymorphism may affect pathogenesis through altering peptide-dependent features of the HLA-B27 molecule. To establish the effect of natural ERAP1 polymorphism on the HLA-B27 peptideome, we immunopurified HLA-B*27:04-bound peptides from 4 lymphoid cell lines with different ERAP1 variants. The peptide pools were subjected to HPLC fractionation and comparatively analyzed by MALDI-TOF MS. Peptide sequencing was carried out by MALDI TOF/TOF MS/MS. Ligands were compared on the basis of their relative abundance and the susceptibility of N-terminal flanking and P1 residues to ERAP1 trimming was quantified.

Results: Pairwise comparisons of HLA-B*27:04-bound peptides from cells expressing different natural variants of ERAP1 revealed significant differences in the size and length of many ligands as a function of their relative expression in the cell lines compared, and in HLA-B27 stability. AS-protective ERAP1 polymorphisms lead to longer peptides and decreased HLA-B27 destabilization, consistent with lower enzymatic activity. Peptides predominant in the context of AS-protective variants showed higher susceptibility of their N-terminal flanking residues to ERAP1 revealing the basis for the effects of this enzyme on HLA-B27.

Conclusion: Our results indicate a general quantitative effect of ERAP1 polymorphism on the HLA-B27 peptideome and suggest that the mechanism of ERAP1/HLA-B27 interaction is a variant-dependent alteration in the balance between epitope generation and destruction, which is determined by the susceptibility of N-terminal flanking and P1 residues to trimming by distinct ERAP1 variants.

SO3

ENDOPLASMIC RETICULUM AMINopeptidase 1 INTERACTION WITH HLA B27 INFLUENCES THE UNFOLDED PROTEIN RESPONSE

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Introduction: We have reported a functional interaction of ERAPI with alteration in MHC-I free heavy chain and HLA-B27-peptide presentation. Here we report the influence of ERAPI on unfolded protein response (UPR) genes in HLA B27 transgenic mice (B27tg).

Methods: B27tg were developed on a MHC double knock out (DKO) strain lacking endogenous murine class I MHC. These mice were crossed with ERAPI-/-/ mice to generate the HLA-B27-ERAPI/KO mice (B27tgE-). Mesenteric lymph nodes (MLN), spleen and liver were obtained from age-matched B27tg and B27tgE- before and 5 days after intra-gastric Yersinia infection. Yersinia enterocolitica 0.8 was delivered to the mice by intragastric tube at a dose of 10^7 organisms. RNA was extracted from tissues and subjected to quantitative PCR with primers specific for the following markers of UPR: Bip, CHOP, XBPI and GADD45. β-actin expression was used as a control.

Results: There was consistent expression of all 4 genes of UPR in the tissues tested except the GADD45 expression in the spleen. In the liver which has the highest expression of ERAPI, the UPR genes were expressed at significantly higher levels in the B27tgE- compared to B27tg. The fold expression of the respective genes in the B27tg vs B27tgE- were; Bip (1.5 4 vs 30.2), CHOP (3.05 vs 4.9), XBPI-1 (19.9 vs 53.9) and GADD45 (7.6 vs 12.2). The fold expression of ERAPI variants in the spleen were comparable between B27tg and B27tgE-: Bip (1.84 vs 1.70), CHOP (2.41 vs 2.20), XBPI (3.79 vs 3.52). MLN demonstrated higher expression of UPR genes in B27tg compared to B27tgE-: Bip (2.07 vs 1.21), CHOP (1.96 vs 1.52), XBPI-1 (2.78 vs 1.22), GADD45 (3.20 vs 1.27). Following Yersinia infection, there was a downregulation of the UPR response genes, seen in both strains. In MLN and spleen, the degree of downregulation of UPR genes was comparable. However, in the liver the decrease in CHOP and XBPI-1 following infection was significantly more pronounced in the B27tgE- (CHOP: 2.20 to 1.55 and XBPI-1: 3.52 to 1.16) than in the B27tg (CHOP: 2.41 to 2.04 and XBPI-1: 3.79 to 3.02).

Conclusions: ERAPI-B27 interaction can result in functionally significant alterations of the UPR.

SO4

IDENTIFICATION OF ROBUST AND DISEASE-SPECIFIC STROMAL ALTERATIONS IN SPONDYLOARTHROPATHY SYNOVITIS

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Introduction/Aim: The cellular and molecular pathways driving synovial inflammation and stromal remodeling in spondyloarthritides (SpA) remain largely unknown. As SpA and rheumatoid arthritis (RA) show clearly distinct patterns of structural remodeling, we conducted this study to identify molecular pathways specific for SpA synovitis by gene expression profiling of the inflamed synovial tissue in both conditions.

Materials and Methods: Synovial biopsies were obtained by arthroscopy. Top differentially expressed genes were validated on three independent cohorts of patients by qPCR and immunohistochemistry. qPCR was also performed on paired SpA synovial biopsies before and after TNF blockade. Synovial fibroblasts and tissue biopsies were used for ex vivo cultures.

Results: The microarray analysis identified a signature set of genes that discriminated with high certainty between SpA and RA. This data was robust and reproducible, as was confirmed by qPCR in the same samples as well as in an independent cohort of early, untreated patients, with some of genes being more than 100-fold upregulated. The gene signature was also consistent as pathway analysis revealed that top-ranking upregulated transcripts in SpA were related to myocyte/myofibroblast biology. Analysis of gene versus SpA samples revealed that these genes were specifically upregulated in SpA rather than downregulated in RA. Most interesting, analysis of paired samples before and after treatment of the patients indicated that this signature was not altered by effective TNF blockade. Immunofluorescence confirmed a marked presence of myofibroblasts in SpA synovitis. Preliminary data suggest that regulation of transdifferentiation of synovial fibroblasts towards myofibroblasts is induced by PDGF and TGFβ. Finally, targeting myofibroblasts with a specific inhibitor of the PDGFR-α tyrosine kinase imatinib mesylate in ex vivo tissue cultures led to a significant decrease in the production of pro-inflammatory cytokines.

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SO5
AUTOANTIBODIES AGAINST CLASS II-ASSOCIATED INVARI-
ANT CHAIN PEPTIDE (CLIP) IN SPONDYLOARTHRITIS
Baarlenken N.T., Nethold S., Stummvoll G.H., Sieper J., Radulawetz M., Reuter S., Matthias T., Schmidt R.E., Witte T.
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Introduction and Aim: Establishing the early diagnosis of spondyloarthritis (SpA) is difficult, since abnormalities in conventional X-ray develop with a latency of several years and only HLA-B27 has been established as a laboratory marker. With the exception of MRI, there are no sufficient tools for the early diagnosis of SpA. The aim of our study was to identify new autoantibodies as diagnostic markers of SpA.

Patients and Methods: As a screening procedure, we used protein array technology for detection of autoantigens in ankylosing spondylitis (AS). Then the results of the protein array were confirmed by ELISA using class II-associated invariant chain peptide (CLIP) domain of CD74 as antigen. Sera for the ELISA were obtained from patients with axial (n=156) and peripheral (n=60) SpA, psoriatic arthriti-
sis without axial involvement (PsA) (n=40), RA (n=80), SLE (n=40), HIV infection (n=60), and blood donors. All donors provided informed consent for the study (ethics number 4928).

Results: Using protein arrays, we detected IgG antibodies against CD74 in 4/5 SpA sera. Using ELISA, IgG autoantibodies against the extracellular CLIP domain of CD74 were found in 56/58 (97%) of SpA patients with a duration of inflammatory back pain of less than 1 year. In control groups, the prevalence of IgG autoantibod-
ies against CLIP was 18/40 (45%) in PsA, 9/80 (11%) in RA, 6/40 (15%) in SLE, 1/40 (2.5%) in HIV and 1/125 (0.8%) in blood donors.

Conclusion: Due to their high specificity and sensitivity, antibodies against the CLIP-domain of CD74 provide an important additional tool for diagnosis of SpA.

SO7
THE EFFECT OF BIOLOGICAL THERAPY ON WORK PARTICI-
PATION IN ANKYLOSING SPONDYLITIS PATIENTS: A SYSTEM-
ATIC REVIEW
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Aim: To systematically review the effect of treatment with biologicals in ankylos-
ing spondylitis on three areas of work-outcomes: employment status, absence from paid work and at-work productivity loss.

Patients and Methods: A systematic search was performed in Pubmed, Embase and the Cochrane Library (up until 15 June 2011) by two authors to identify relat-
eval articles. Quality of included studies was assessed by two authors using the Dutch Cochrane guidelines for (un)controlled cohorts and randomised controlled trials (RCTs). Data were extracted by one author and checked by another using a self-composed form. Due to extensive inter-study heterogeneity, narrative summa-
rizes were used to present the data.

Results: Nine studies were included (six uncontrolled cohorts, one population controlled cohort and two RCTs) that reported on 39 comparisons. Overall 961 patients were treated with three different TNF-α inhibitors (etanercept, infliximab, adalimumab). For presenteeism and absence from work, most comparisons showed improvement in favour of biologicals, but not all comparisons were statistically sig-
nificant and they usually concerned before-after analyses. For employment status, changes were less often positive, but studies addressed patients with longstanding AS, lacked power and were of relatively short follow-up.

Conclusion: Although trends towards beneficial effects of biological in longstanding AS were seen on all work outcomes, this effect proved often not significant, when compared to the untreated group or to baseline. Since the majority of studies were (extensions of) controlled trials, the generalizability of the effect of biologi-
cals on work participation in real life should be further studied in larger (population controlled) studies. The effect of biologicals in patients with early disease has not been addressed as yet.

SO6
LOW SCLEROSTIN LEVELS: A PREDICTIVE MARKER OF PER-
SISTENT INFLAMMATION IN ANKYLOSING SPONDYLITIS DURING ANTI-TNF THERAPY?
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Introduction: Sclerostin levels have been reported to be low in ankylosing spondyl-
itis (AS), but there is no data regarding the possible role of this Wnt inhibitor dur-
ing anti-TNF therapy.

Aim: The present study longitudinally evaluated sclerostin levels, inflammatory markers and bone mineral density (BMD) in AS patients under anti-TNF therapy.

Material and Methods: Thirty active AS patients were assessed at baseline, 6 and 12 months after anti-TNF therapy regarding clinical parameters, inflamma-
tory markers, BMD and baseline radiographic damage (mSASSS). Thirty age- and sex-matched controls consented to the approved Ethics Committee (ethics number 4928).

Results: At baseline, 10 patients with high CRP (>5mg/l) compared to the other 20 patients with normal CRP (p=0.004). Of note, these 10 patients with persistent inflammation also had lower sclerostin serum levels at baseline compared to the other patients (p=0.023).

Conclusion: Persistent low sclerostin levels may underlie continuous inflammation in AS patients under anti-TNF therapy.

SO8
BRAIN MRI AND PSYCHOPHYSICAL ANALYSIS DEMONSTRATE NEUROPATHIC PAIN TO BE A COMPONENT OF BACK PAIN IN ANKYLOSING SPONDYLITIS
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Introduction/Aim: The mechanisms underlying pain in ankylosing spondylitis (AS) are unclear. The aim of this study was to investigate whether there is a neuro-
pathic component in AS pain and to delineate gray matter brain abnormalities as-
sociated with AS.

Materials and Methods: Seventeen patients with back pain secondary to AS (12M/5F; 34±12.4yo) and age/sex-matched controls consented to the approved study. Mean BASDAI scores in the AS patients were 6.6±2.1, and none were on biologic agents at the time of the study. Patients were assessed with the Pain-
DETECT (scores <12 indicate low probability of neuropathic pain) and McGill Pain Questionnaires. Mechanical and thermal pain thresholds were determined, 3T MRI scans obtained for all subjects. Brain gray matter was measured with cortical thickness analysis (Freesurfer) and voxel based morphometry (FSL-VBM) for sub-
cortical structures with age included as a covariate.

Results: The mean painDETECT score in AS patients was 15.1±7.08 (eleven scored >12). Compared to controls, AS patients had significantly decreased me-
chanical and cold sensitivity on their dorsal feet but pain thresholds were not ab-
normal. The gray matter analysis identified that AS patients had significant cortical thinning in left primary sensory (S1), insular, and anterior mid-cingulate cortices (MCC), and right supplemental motor area and ACC. Furthermore, painDETECT scores correlated with cortical thinning in the left S1 and thickening in the left
motor cortex, right anterior cingulate and prefrontal cortex. All cortical findings were significant at p<0.05 image-wise, corrected for multiple comparisons.

Conclusions: Our psychophysical testing and self-reports identified signs of neuropathy. The imaging results of abnormal brain gray matter linked to neuropathic pain are concordant with the clinical picture of AS having sensorimotor and mood deficits as well as neuropathic pain. These data suggest that back pain in AS is a mixed pain condition that includes a neuropathic pain component.

SO9

EFFICACY AND SAFETY OF ADALIMUMAB IN PERIPHERAL SPONDYLARTHRITIS PATIENTS: RESULTS FROM ABILITY-2

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Introduction/Aim: ABILITY-2 is the first randomized, controlled trial to use the ASAS peripheral SpA criteria to evaluate efficacy and safety of adalimumab (ADA) in peripheral SpA patients not diagnosed with psoriatic arthritis (PsA) or anklyosing spondylitis (AS).

Methods: In the ongoing ABILITY-2 study, patients with peripheral SpA, not diagnosed with PsA or AS, and inadequate response to NSAIDs, were randomized to ADA or placebo for 12 weeks. Peripheral SpA response (pSpARC40): ≥40% improvement in Patient Global Assessment (PGA) and PGA-pain and ≥40% improvement in 2 of the following: SJC and TJC, Enthesitis Count, or Dactylitis Count, was assessed at week 12.

Results: Baseline characteristics were similar, except mean age was higher (43 vs 39 years) and percentage of patients with dactylitis count >0 was lower (16% vs 30%) in the ADA group. At week 12, the percentages of ADA patients achieving pSpARC40 and other efficacy endpoints were higher vs placebo (Table). AEs were similar (ADA/placebo): serious AEs (1.2%/1.2%), infectious AEs (21.4%/28.4%); no serious infections, tuberculosis, or malignancies occurred.

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>ADA</th>
<th>PBO</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pSpARC 40, %</td>
<td>39.3</td>
<td>19.8</td>
<td>.006</td>
</tr>
</tbody>
</table>

Secondary endpoints (mean change)
PGA (VAS 0–100, mm)    -27.5| -16.4| .003
PGA pain (VAS 0–100, mm) -28.9| -17.1| .001
PGAC (VAS 0–100, mm)   -32.2| -18.2| <.001
TJC (0–78)            -5.9| -1.8| <.001
SJC (0–76)            -3.6| -3.1| .045
Lees enthesis index (0–6) -0.8| -0.1| <.001
SPARCC enthesis index (0–16) -1.7| -0.7| <.001
Dactylitis count (0–20) -0.2| -0.3| .808
BASDAI9            -2.1| -1.0| <.001
HAQ-S score9          -0.3| -0.2| .051
SF-36v2 PCS3            6.7| 2.4| <.001

Conclusions: ADA was well-tolerated and improved signs, symptoms, and physical function in non-PsA, non-AS peripheral SpA patients, suggesting ADA can be a treatment option for peripheral SpA patients with inadequate response to NSAIDs.

SO11

MRI INFLAMMATION AND ITS RELATION WITH MEASURES OF CLINICAL DISEASE ACTIVITY AND DIFFERENT TREATMENT RESPONSES IN PATIENTS WITH ANKYLOSING SPONDYLITIS TREATED WITH A TNF INHIBITOR

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Aim: To investigate the relationship between MRI inflammation and measures of clinical disease activity as well as treatment responses in patients with anklyosing spondylitis (AS) treated with a TNF inhibitor.

Methods: In an 80% random sample of the ASSERT database, MRIs at baseline (n=221), week (wk) 24 (n=158, infliximab group) and wk102 (n=179, all patients) were scored by 2 independent readers (Berlin scoring system). Spearmann correlation coefficients were determined. For each treatment regimen (in thousands) up to January 1 of 2017 and 2032 were 242.64 and 878.80 in Scenario 1, and 248.36 and 878.80 in Scenario 2, respectively. Conclusions: This real time modelling approach is feasible and provides comprehensive information for the decision makers not only on cost-effectiveness at the patient-level but also on the total health and societal budget impacts at the population level at specific points in calendar time. The model is also useful for the clinicians who wish to get insight into how their practice affects the health burden of the society.

Reference:

Conclusions: Despite rapid methodological development, modelling strategies in health economic evaluation are still insufficient in providing comprehensive information expected by decision makers such as actual numbers of patients in a society receiving a new technology and health burden and expenditure at different points in calendar time. Simultaneously predicting burden of illness and cost-effectiveness of complex treatment strategies for rheumatic diseases in a real context of a society has not yet been done.

Objectives: This study aimed at developing a simulation model to predict impact of treatment strategies for a chronic disease in a real society on population health, budgets and cost-effectiveness at specific points in calendar time. Two scenarios regarding treatment of all patients with anklyosing spondylitis (AS) in the Dutch population were used as a case. In Scenario 1, five NSAIDs were available and in Scenario 2, five NSAIDs and two anti-TNFs.

Methods: The discrete event modelling framework developed by Tran-Duy et al.1 was adapted and used in this population dynamic simulation. Distinguishing the prevalent AS population on January 1, 2012 and the incident AS cohorts in the subsequent 20 years, the model tracked individually an actual number of AS patients until death or end of the simulation time. During the simulation, data on patient characteristics, costs and health at discrete points in calendar time were generated. The model was written using the Delphi programming language. Data analysis was done using R.

Results: The predicted size of prevalent AS in the Dutch society varied from 69350 to 70540 with 31–33% of the patients receiving anti-TNFs over the period 2012-2032. Incremental costs per QALY gained in Scenario 1 (in thousands) on January 1 of 2017 and 2032 would be 130.66 and 86.70, respectively. Cumulative total societal costs (in billion Euros) up to January 1 of 2017 and 2032 would be 10.66 and 16.88 in Scenario 1, and 11.41 and 18.48 in Scenario 2, respectively. Anti-TNFs would result in higher annual drug costs, but lower annual productivity and non-drug health care costs. Cumulative total population QALYs (in thousands) up to January 1 of 2017 and 2032 were 242.64 and 860.08 in Scenario 1, and 248.36 and 878.80 in Scenario 2, respectively.

Conclusions: This real time modelling approach is feasible and provides comprehensive information for the decision makers not only on cost-effectiveness at the patient-level but also on the total health and societal budget impacts at the population level at specific points in calendar time. The model is also useful for the clinicians who wish to get insight into how their practice affects the health burden of the society.
Conclusions: MRIa correlates better with CRP than with other measures of disease activity. By including both CRP and patient-reported outcomes in its formula, ASDAS has the advantage of providing combined information on objective and subjective measures. As a status and response measure ASDAS better reflects the spinal inflammatory disease process in AS than other composite measures.

SO12 SECUKINUMAB SIGNIFICANTLY IMPROVES ASAS20 RESPONSES VERSUS PLACEBO IN MODERATE-TO-SEVERE ANKYLOSING SPONDYLITIS PATIENTS

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Introduction: This proof-of-concept study assessed the preliminary efficacy and safety of secukinumab, a fully human monoclonal antibody targeting IL-17A for treatment of moderate-to-severe ankylosing spondylitis (AS).

Methods: Patients (n=30) with active AS randomly (4:1) received two i.v. infusions of secukinumab 10mg/kg or placebo, given 3 weeks apart. Primary endpoint was proportion of patients achieving ASAS20 response at Week 6. Historical placebo information from 8 AS trials was included in a Bayesian analysis of primary endpoint.

Results: Baseline characteristics were comparable between groups. 5 patients (placebo; 3, secukinumab 2) discontinued the study before Week 6. At Week 6, 61% (14/23) secukinumab-treated patients achieved ASAS20 responses vs 17% (1/6) on placebo (99.8% probability of positive treatment difference; 95% credible interval of response difference [12%, 56%]). At Week 6, ASAS40 and ASAS5/6 response rates of secukinumab-treated patients were 30% and 35%, respectively, mean (range) BASDAI change from baseline was -1.8 (-5.6-0.8). ASAS response rates were greater at Week 6, and declined thereafter till Week 28, consistent with preliminary dose regimen. Post-hoc subgroup analyses showed TNFi naive patients have improved HLA-B27/Human β2 Microglobulin (Hu β2m) control rats were used. Six week old rats were immunized with 30, 60 or 90 μg M. tuberculosis induced arthritis and histological.

Results: In vitro stimulation with IL-10 induced CD163-expression on macrophages, mimicking the phenotype in SpA synovitis. Although the expression of tmTNF was not increased in IL-10 polarized macrophages in comparison with IFN-γ and IL-4 polarized cells, the production of sTNF was clearly impaired in the IL-10 polarized macrophages, indicating a relative shift from sTNF to tmTNF. Moreover, the sTNF SF levels were significantly lower in SpA compared to RA despite similar TNF mRNA levels in ST. This was not related to altered expression of TNF receptors or a decrease in TACE mRNA levels. To investigate whether over-expression of tmTNF could be relevant in SpA pathophysiology, we characterized tmTNF transgenic mice. As previously described, these mice develop a moderate arthritis with 100% incidence, resulting in deformation and loss of grip strength. Histologically, the joints were characterized by moderate synovitis, appearance of lymphoid aggregates in bone marrow and osteoproliferation. They also developed spontaneously spondylitis as evidenced by a crinkled tail and histological inflammation and osteoporofloration.

Conclusions: tmTNF is relatively overexpressed by CD163+ macrophages in SpA synovitis and leads to a SpA phenotype in transgenic mice.

P2 INNATE IMMUNE STIMULATION TRIGGERS EXPERIMENTAL SPONDYLOARTHRITIS IN HLA-B27/HUMAN BETA 2 MICROGLOBULIN TRANSGENIC RATS

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Introduction: Spondylarthritls (SpA) is driven by altered innate immune responses rather than by autoantigen-specific T or B cell responses. This study aimed to test directly the hypothesis that stimulation of the innate immune system triggers experimental SpA.

Methods: An immunization strategy with Mycobacterium tuberculosis was used to test this hypothesis; although comparable to adjuvant-induced arthritis, much lower concentrations were used. The improved HLA-B27/Huβ2m (with a high copy number of human beta 2 microglobulin (Huβ2m(2)) and appropriate HLA-B7/ Huβ2m control rats were used. Six week old rats were immunized with 30, 60 or 90 μg M. tuberculosis in IFA. Arthritis and spondylitis were monitored clinically and histologically.

Results: In non-immunized conditions, only HLA-B27/Huβ2m tg males spontaneously develop arthritis and spondylitis after 4-6 months of age reaching an incidence of 70% and 40% respectively. In males, 30 μg M. tuberculosis induced arthritis and/or spondylitis in 5/6 HLA-B27/Huβ2m animals, but in none of the controls. In females, 60 or 90 μg M. tuberculosis induced both arthritis and spondylitis in all HLA-B27/Huβ2m tg rats, but in none of the controls. Arthritis in females appeared 2-3 weeks after immunization in both males and females. Moreover, the pathophysiology of this inducible model is comparable to the spontaneous disease induction in HLA-B27/Huβ2m tg males, resulting in destructive infiltration, and also new bone remodeling both in peripheral joints as in the tail vertebrae.
P3

A REVERSE INTERFERON-γ SIGNATURE IS SHARED BY CD103+CD4+ DENDRITIC CELLS FROM HLA-B27 TRANSGENIC RAT AND MACROPHAGES FROM ANKYLOSING SPONDYLITIS PATIENTS

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Introduction: In HLA-B27/human β2-microglobulin transgenic rat, the spontaneous development of an ankylosing spondylitis-like disease (AS) strongly correlates with high transgene expression and dendritic cells (DCs) dysfunction. Aim: To investigate DCs’ dysfunction, transcriptomic analysis was conducted on HLA-B27 DCs and results compared to those from monocyte-derived macrophages from AS patients (Arthritis Rheum 2008;58:1640).

Materials and Methods: CD103+CD4+DC samples were magnetically-sorted (60-80% purity) from spleens of 3 groups of age-matched male rats (8 pool of HLA-B27 in progeny of Tg and WT and 2 independent lines). Gene expression analysis was performed using Affymetrix Rat230_2 GeneChip (31100 probe-sets) and used for the transcriptomic assay. Statistical analysis were done using Student’s t-test. p-values were filtered at 5% and only fold changes ≥ 1.5 were kept. These data were compared to published gene expression analysis from macrophages of 8 AS patients and 9 healthy controls and the sum of all data submitted to hierarchical clustering. Selected genes were validated using RT-PCR from FACS-sorted cells (96-99% purity).

Results: Rat microarray analysis revealed significant differential expression of 178 genes in HLA-B27 DCs. Among these genes, 45 (25.3%) were interferon-γ-regulated (IFNγ) and interestingly 30 of them known to be upregulated were underexpressed in HLA-B27 DCs, indicating a reverse IFNγ signature (fold changes: 0.02-0.66). Further RT-PCR analysis validated selected candidate genes (STAT1, IFIT2, IRF7, CXCL9-10-11). The meta-analysis between rat and human data revealed 5 shared IFNγ-regulated genes: IRF1, STAT1, CXCL9-10 and IFIT3.

Discussion: This study reveals consistent differences in gene expression patterns between HLA-B27 rats and AS patients and highlights an unexpected reverse IFNγ signature. These results suggest that HLA-B27 expression could lead to defective IFNγ signaling which would participate in pathogenesis.

P5

BONE MICROARCHITECTURE IN ANKYLOSING SPONDYLITIS IN RELATION TO LUMBAR OSTEOPOROSIS, VERTEBRAL FRACTURES AND SYNDYMOSYPHYTE FORMATION

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Introduction and Aims: Bone microarchitecture can since the development of high resolution peripheral quantitative computed tomography (HRpQCT) be studied in vivo in the similar detail as in bone biopsies. Our aims were to compare volumetric bone mineral density (vBMD) of trabecular and cortical bone in central and peripheral skeleton and to study the relation between bone microarchitecture, vertebral fractures and syndysmophyte formation in AS.

Patients and Methods: HRpQCT of ultradistal radius and tibia and QCT of lumbar spine were performed. vBMD was measured in trabecular and cortical bone separately. Spinal radiographs were acquired for the assessment of vertebral fractures and syndysmophyte formation (mSASSS).

Results: 69 male AS-patients (NW-criteria) with age (meansD) 49±15 yrs, symptoms duration 23±4 yrs and BAIAD3 ±1±2 were included. Strong correlations were found between trabecular vBMD in lumbar spine, radius (r=0.762; p<0.001) and tibia (r=0.712; p<0.001). Low spinal trabecular vBMD was significantly associated with worse values of most microarchitectural parameters, except trabecular number. Patients with vertebral fractures (n=88) had significantly lower lumbar trabecular (-26%; p=0.038) and cortical (-17%; p=0.011) vBMD. Peripheral trabecular vBMD, cortical thickness, trabecular thickness and separation were also significantly worse in patients with vertebral fractures (-24% to 16%). Low cortical thickness of tibia was the strongest risk factor for vertebral fractures in multivariate analyses. mSASSS correlated negatively with trabecular thickness (r=0.488; p<0.001) and trabecular vBMD in both peripheral skeleton (r=0.475; p=0.001) and lumbar spine (r=0.620; p<0.001). Adjusting for age syndysmophyte formation was significantly associated with decreasing trabecular vBMD, but increasing cortical vBMD in lumbar spine, however not with increasing cortical thickness/density in the periphery.

Conclusion: Lumbar osteoporosis and vertebral fractures were associated with lower vBMD and worse microarchitecture in peripheral skeleton. The results indicate that osteoporosis is a systemic process in AS, whereas the pathologic new bone formation is local and confined to the central skeleton.

P6

DKK1 SERUM LEVEL IS INCREASED IN RECENT SPONDYLOARTHITIS AND IS ASSOCIATED WITH HIGHER PREVALENCE OF SYNDYMOSYPHYES - DATA FROM THE DESIR COHORT

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Background: Dickkopf-1 (DKK-1) is an inhibitory protein of the Wnt signalling pathway that could radically be involved in the osteoblastogenesis associated with syndysmophyte construction.

Objectives: To investigate the DKK-1 serum levels among patients with recent inflammation back pain (IBP) fulfilling ASAS criteria for spondyloarthritis (SpA) and to investigate the parameters associated or correlated with DKK-1 increase.

Methods: The DESIR cohort is a prospective, multicenter French cohort of patients with early IBP suggestive of SpA, including 708 patients. DKK-1 serum levels were assessed at baseline on the whole cohort by sandwich ELISA (Biomedica, Vienna). DKK-1 serum levels were analyzed in the subgroup of SpA patients (N=479; 68.9%) and compared with 71 controls. All SpA patients were naive of any TNF-blocker at inclusion in the study. Univariate and multivariate analyses

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Conclusions: These data indicate that innate immune activation triggers experimental SpA in HLA-B27/HuI2m tg rats. Moreover, a low dose of M. tuberculosis increases incidence and accelerates and synchronizes disease onset, which will facilitate further use of this model for experimental and preclinical research.

but rSOST–treated PGISp mice showed increased SOST suggesting the rSOST was targeting the joints. No changes were seen in BMD byDEXA. Vertebral disease was assessed histologically at the termination of the study and 8 weeks of rSOST treatment showed no effects on disease severity or incidence possibly due to SOST levels not regaining normal values.

Discussion: Although no change in disease severity was seen, this pilot study has demonstrated stability of rSOST in vivo and activity in affected joints. Future studies will utilize higher rSOST doses and a longer time course of treatment.
were performed in order to identify the main predictors of serum DKK-1 level in SpA patients. Results: Serum DKK-1 levels were significantly increased among the 479 SpA patients (mean ± SEM 35.4 ± 1.6 pmol/L) compared with controls (10.8 ± 1.1 pmol/L) (p < 0.0001). DKK-1 serum levels were significantly correlated with ESR (p = 0.04; r = 0.10), CRP (p = 0.015; r = 0.11), hs-CRP (p = 0.01; r = 0.12), ASDAS-ESR (p = 0.03; r = 0.10), ASDAS-CRP (p = 0.016; r = 0.11). DKK-1 serum levels were significantly higher among SpA patients with axial structural changes (mSASSS>0; N=131) (mean ± SEM 35.4 ± 1.6 pmol/L) compared with patients with normal X-Rays (N=334) (mean ± SEM 28.6 ± 1.1 pmol/L) (p < 0.0001). Multivariate analysis led to a significant association of DKK-1 serum levels with the presence of structural changes at baseline (p < 0.0006).

Conclusions: This study conducted in a large cohort of patients presenting with early axial SpA clearly showed an increase in DKK-1 serum levels, such increase being even more important in the subgroup of patients with axial structural changes.

P7

EFFECTS OF HLA-B27 EXPRESSION ON OSTEOCLASTS AND OSTEOBLASTS

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HLA-B27, a major risk factor for spondylarthritides (SpA), is associated with inflammatory bowel disease and formation and inhibition of bone resorption. Key features of the SpA phenotype are recapitulated in HLA-B27 human β2m transgenic (B27-Tg) rats. Since HLA class I is expressed in cells involved in bone homeostasis, we asked whether HLA-B27 expression affects the development and/or function of osteoclasts (OCs) and osteoblasts (OBs). To examine OC formation, BM monocytes (BMMo) derived from healthy B27-Tg, wild type (WT), and B7-Tg control rats, were treated with RANKL or TNF-α, and OCs were quantified by TRAP staining. To examine OB development, calvarial OBs were differentiated in osteogenic medium, and then treated with IFN-γ, TNF-α or both during differentiation. Mineralization was assessed by Alizarin red staining and alkaline phosphatase (ALP) activity. Gene and protein expression was measured by RT-PCR, Western blotting, and/or ELISA.

HLA-B27 promotes OC formation 2.5-fold (p < 0.05) compared to WT or B7-Tg cells, in cultures treated with TNF-α, but not with RANKL. Neutralization of IL-1α abolished the effect of HLA-B27 on enhanced OC formation, and addition of IL-1α to TNF-α-treated WT cells promoted OC formation. Neutralization of IFN-β further enhanced OC formation in B27-Tg cultures. TNF-α upregulated HLA-B27 expression in BMMo, exacerbated misfolding, led to UPR activation, and enhanced IL-1α production. In OBs, TNF-α inhibited mineralization of WT and B27-Tg cells in a dose dependent manner, whereas IFN-β alone had no effect. However, when treated with both cytokines, cells expressing HLA-B27 were refractory to TNF-α mediated inhibition of OB differentiation, and exhibited higher mineralization compared to WT OBs. Our results indicate that HLA-B27 promotes TNF-α induced osteoclastogenesis via enhanced IL-1α production despite the presence of inhibitory IFN-β. In addition, HLA-B27 expressing OBs exposed to IFN-γ are refractory to the inhibitory effects of TNF-α on mineralization. Taken together, these results suggest that HLA-B27 expression may influence the effect of pro-inflammatory cytokines on bone homeostasis. These effects could be highly relevant for SpA pathogenesis and the unique phenotype of this disease.

P8

CORRELATION BETWEEN DISEASE ACTIVITY, FUNCTIONAL CAPACITY, AND HEALTH-RELATED QUALITY OF LIFE OF FILIPINOS WITH ANKYLOSING Spondylitis (PRELIMINARY RESULTS)

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1Dept. of Rheumatology, LUMC, Leiden; 2m transgenic (B27-Tg) females (11-15 years for cutaneous phenotype of this disease.

Introduction and Aim: Disease activity in ankylosing spondylitis (AS) generally aimed to describe the clinical profile of Filipinos with AS, as well as their disease activity, functional capacity, and HRQoL. Disease activity was then correlated with functional capacity and HRQoL.

Materials and Methods: Filipino patients with diagnosed AS were recruited from different arthritis clinics in Metro Manila. Disease activity was measured using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), while functional capacity and HRQoL were measured using the Bath Ankylosing Spondylitis Functional Index (BASFI) and Short Form (SF)-36, respectively. Pearson’s correlation was used to analyze the relationship between BASDAI and BASFI, and between BASDAI and SF-36.

Results and Discussion: Twenty-four patients entered the study. Mean age was 35.7 ± 12.7 years and mean age at diagnosis was 31.1 ± 12.9 years. Symptoms occurred for a mean of 9.6 ± 9.7 years with mean duration of symptom onset to diagnosis of 3.8 ± 5.4 years. Subjects had mild to moderate disease activity; functional capacity was most impaired in performing a full day’s activities at home or at work. BASDAI was highest in vitality and lowest in emotional role, with mental health components generally showing higher scores than physical health components. Pearson’s correlation showed moderate positive correlation between BASDAI and BASFI (r=0.6016, p=0.0012) and moderate negative correlation between BASDAI and the physical health domain (r=-0.6916, p=0.0001) and mental health domain (r=-0.3575, p=0.0863) of SF-36. However, only the first two correlations were statistically significant.

Conclusion: A significant positive correlation was found between BASDAI and BASFI scores, and a significant negative correlation between BASDAI and physical health domain scores of SF-36. Thus, Filipino AS patients with higher disease activity have more functional disability and poorer physical HRQoL.

P9

THYROID DYSFUNCTION IS MARKED IN PATIENTS WITH PSORIATIC ARTHRITIS (PsA)

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Introduction: Whereas autoimmune thyroiditis is associated to rheumatic diseases (ex:SLE, SJögren’s, RA), few controversial studies have assessed thyroid involvement in PsA. Aim: To evaluate thyroid function and serum thyroid antibodies antithyroglobulin (TGA) and antithyroidperoxidase (AbTPO) in patients with PsA searching for clinical associations in relation to PsA subtypes.

Patients and Methods: Subjects fulfilling CASPAR criteria for PsA were consecutively enrolled and interviewed after approval of local ethics committee. Additional clinical data were obtained by specific questionnaire and extensive chart review. Patients were classified in five subgroups according to Moll/Wright PsA subtype. Patients and Methods: Subjects fulfilling CASPAR criteria for PsA were consecutively enrolled and interviewed after approval of local ethics committee. Additional clinical data were obtained by specific questionnaire and extensive chart review. Patients were classified in five subgroups according to Moll/Wright PsA subtype. Serum TSH, FT4, TPOAb and TgAb levels were determined by routine laboratory analysis and tested by AutoDELFIA immunoassay (PW-USA). Statistical significance was considered if P<0.05.

Results: Eighty PsA patients, 39M (48.8%), 41F (51.3%), mean age=52years (20-83±14yrs) were included. Mean disease duration was 17±11years for cutaneous psoriasis (1-50) and 12±8years for arthritis (1-49). Twenty-seven (34%) patients had symmetric polyarthritis, followed by 21 (26.3%) oligoarticular, 21 (26.3%) axial, 7 (6.5%) mutilans and 6 (6.5%) classical PsA. Remarkably, 8 (22%) patients had thyroid dysfunction: 9 (11.5%) hypothyroidism, 6 (7.5%) subclinical hypothyroidism and 3 (3.7%) subclinical hyperthyroidism. Thyroid autoantibodies were positive in 22/80 (27.5%) patients’ sera: 3 (3.7%) TPOAb+, 12 (15%) TgAb+, 7 (8.7%) AbTPO+ and TGA+. Four of 18 patients with thyroid dysfunction (22.2%) had sera anti-thyroid antibodies: 1 TPOAb and 3 TGA. Mean age, sex, race, distribution, ethic, tabagism, PsA subtype, thyroid antibodies and ANA positivity were alike among patients with thyroid dysfunction and those with normal thyroid function. Remarkably, family history for cutaneous psoriasis was higher in patients with hypothyroidism compared to those with normal thyroid function (40 vs 11%, p<0.015).

Conclusions: Thyroid dysfunction and self-organ-specific antibodies in almost one fourth of PsA patients, mostly related to familiar cutaneous disease indicate the need of routine clinical thyroid evaluation as part of PsA patients’ approach, in order to enable adequate care and specific prompt treatment.

P10

HOW USEFUL IS IMAGING OF THE SI-JOINTS (MRI AND/OR X-RAY) IN PATIENTS WITH POSSIBLE SPONDYLOARTHRITIS (PsA) IN THE DIAGNOSTIC WORK-UP?

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Introduction/Aim: In daily practice, the diagnostic work-up of patients with possible spondylarthritides (xSpA) starts with clinical and laboratory data. In many patients MRI and/or X-rays of the SI-joints (MRI-SIJ, X-SIJ) is performed. What is the contribution of imaging in confidently diagnosing (possible) axSpA patients?

Results: Twenty-four patients entered the study. Mean age was 35.7 ± 12.7 years and mean age at diagnosis was 31.1 ± 12.9 years. Symptoms occurred for a mean of 9.6 ± 9.7 years with mean duration of symptom onset to diagnosis of 3.8 ± 5.4 years. Subjects had mild to moderate disease activity; functional capacity was most impaired in performing a full day’s activities at home or at work. BASDAI was highest in vitality and lowest in emotional role, with mental health components generally showing higher scores than physical health components. Pearson’s correlation showed moderate positive correlation between BASDAI and BASFI (r=0.6016, p=0.0012) and moderate negative correlation between BASDAI and the physical health domain (r=-0.6916, p=0.0001) and mental health domain (r=-0.3575, p=0.0863) of SF-36. However, only the first two correlations were statistically significant.

Conclusion: A significant positive correlation was found between BASDAI and BASFI scores, and a significant negative correlation between BASDAI and physical health domain scores of SF-36. Thus, Filipino AS patients with higher disease activity have more functional disability and poorer physical HRQoL.

Poster Presentations
Patients and Methods: Patients with chronic back pain (≥3 months, n=2 years, onset <45 years) in the SpondyloArthritis Caugh Early (SPACE)-cohort underwent a fixed protocol. First, medical history, physical examination and laboratory assessments, including HLA-B27 typing, were performed. A rheumatologist experienced in SpA diagnosed all patients as either SpA or no-SpA with a level of confidence (scale 0 [not confident at all] to 10 [very confident]). Second, imaging (MRI-SIJ, X-SIJ) was performed and the same rheumatologist diagnosed all patients again with a new level of confidence. For the analyses, cut-off values of ≥5 (not confident) and ≥6 (confident) were used. Results: In 52/157 patients (31%), the rheumatologist was confident about the diagnosis based on clinical and laboratory data only (SpA n=51), no-SpA (n=21). Imaging was positive in 32/157 patients (20.4%). In 3/52 patients (5.7%) the rheumatologist was confident about the diagnosis no-SpA, but revised the diagnosis into confident SpA after imaging. In 95/52 patients (17%), the rheumatologist was confident about the diagnosis based on clinical data only, but was not confident anymore after receiving negative imaging. Initially, the rheumatologist was not confident about the diagnosis in 105/157 patients (67%). After imaging, the rheumatologist was confident about the diagnosis in 73/105 patients (SpA n=24; 29%), no-SpA (n=52; 50%). In the remaining 32 patients (30%) imaging did not change confidence, nor diagnosis (table).

Conclusions: Imaging (MRI-SIJ and/or X-SIJ) is useful for the rheumatologist in the large majority of patients with possible axSpA, except for the patients in which the rheumatologist is confident about the diagnosis of SpA before imaging.


van den Berg R.1, de Hooge M.1, van Gaalen F.1, de Hooge M.2, van der Heijde D.1, Huizinga T.1, van der Heijde D.1, van Gaalen F.1, Reijnierse M.1, Huizinga T.1, van der Heijde D.1, 1Dept. of Rheumatology, LUMC, Leiden; 2Dept. of Radiology, LUMC, Leiden, The Netherlands

Introduction/Aim: It is possible to classify patients as axial spondylarthropathy (axSpA) according to the ASAS axSpA criteria HLA-B27-arm without any signs of sacroiliitis on MRI or X-ray. The question arises whether patients fulfilling the HLA-B27-arm reflect a group of patients similar to those fulfilling the imaging-arm of the ASAS axSpA criteria. Therefore, patients fulfilling the HLA-B27-arm and patients fulfilling the imaging-arm are compared on demographics, number of SpA-features and level of disease activity.

Patients and Methods: The SpondyloArthritis Caugh Early (SPACE)-cohort is set-up in the Leiden University Medical Center (LUMC) aiming to diagnose and treat patients with axSpA at an earlier stage. Patients with back pain (≥3 months, but ≥2 years, onset <45 years) visiting the rheumatology outpatient clinic were included. All patients of the SPACE-cohort (n=157) fulfilling the ASAS axSpA criteria were included in this analysis (n=60).

Results: Of those 60 patients, 29 fulfilled the imaging-arm (11 fulfilling modified New York (mNY) criteria; 18 MRI positive only) and 31 fulfilled the HLA-B27-arm. Patients fulfilling the HLA-B27-arm have significantly more often a positive family history for SpA (p=0.001), are more frequently female (p=0.04) and have a significantly shorter disease duration (p=0.02). Moreover, there was a trend towards more uveitis (p=0.09). Patients in both arms are very similar with respect to all other SpA-features and level of disease activity (IBDAS and ASDAS). Within the imaging-arm, patients with sacroiliitis on X-ray do not differ significantly from patients with sacroiliitis on MRI in symptom duration, disease activity and presence of SpA-features.

Conclusions: Patients with sacroiliitis on X-ray have the same level of disease activity and symptom duration as patients with sacroiliitis on MRI only. Patients fulfilling the HLA-B27-arm are remarkably similar to patients fulfilling the imaging-arm of the ASAS axSpA criteria, with respect to the presence of most SpA-features and level of disease activity.

P12 IS IT USEFUL TO REPEAT MRI IN THE DIAGNOSTIC WORK-UP FOR SPONDYLOARTHRITIS?

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Introduction/Aim: In the diagnostic work-up of spondyloarthritis (SpA), MRI of the SI joints (MRI-SIJ) is important. One study showed that it might be useful to repeat MRI-SIJ after 1-2 years in HLA-B27-positive male patients. Is it also useful to repeat MRI-SIJ after a period <1 year?

Patients and Methods: Patients with chronic back pain (≤3 months, n=2 years, onset <45 years) in the SpondyloArthritis Caugh Early (SPACE)-cohort underwent MRI-SIJ at baseline. Patients with (possible) SpA (n=90) underwent follow-up MRI-SIJ after 3 months. MRI-SIJ were graded by 3 independent readers (SpA (n=31), no-SpA (n=21)). Two more patients (2.2%) are classified as SpA after developing a positive MRI-SIJ at follow-up. In 4 patients 3-month MRI-SIJ became negative (21.1%).

Variation in MRI-status occurred in 10% of the patients over a 3-month period. Gender and HLA-B27-status are predictive for 3-month MRI-SIJ-positivity. In patients with normal baseline MRI-SIJ, male gender (OR 7.7; 95%CI 2.6-23.1; p=0.001) and good response to NSAIDs (OR 3.5; 95%CI 1.3-9.1; p=0.02) are predictors of 3-month MRI-SIJ-positivity. Gender and HLA-B27-status were used in a multivariate model. Groups were based on this model (table). In the majority of the patients (90%), MRI-status (positive (n=15) or negative (n=66)), did not change over time. Five patients with normal baseline MRI-SIJ developed 3-month MRI-SIJ-positivity (7%). 2/5 fulfilled the ASAS axial SpA criteria only at follow-up. In 4 patients 3-month MRI-SIJ became negative (21.1%).

Only baseline MRI-SIJ positivity, n (%) Only 3-months MRI-SIJ positivity, n (%) Both baseline and 3-months MRI-SIJ positivity, n (%)

<table>
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<td>HLA-B27+, male, n=14</td>
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<td>1 (5.9)</td>
<td>2 (11.8)</td>
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Conclusions: We confirmed that baseline MRI-SIJ-positivity is a strong predictor for follow-up MRI-SIJ-positivity. In patients with normal baseline MRI-SIJ, male gender and HLA-B27-positivity are predictive for 3-month MRI-SIJ-positivity. Variation in MRI-status occurred in 10% of the patients over a 3-month period. Three more patients (2.2%) were classified as SpA after developing a positive MRI-SIJ. More data are needed to decide if it is necessary to repeat MRI-SIJ, and if so, with what time interval.
ALMOST 40% OF PATIENTS WITH CHRONIC BACK PAIN STARTING BEFORE THE AGE OF 45 FULLFILL THE ASAXIAL SPONDYLOARTHROPATHY CRITERIA

Objective:

Methods: All (n=157) patients included in the SpondyloArthritis Caught Early-project (selection criteria: almost daily back pain ≥3 months, ≥2 years, onset ≤45 years) were classified according to modified New York (mNY), European SpA Study Group (ESSG), Amor and ASAS axial SpA classification criteria sets. Results: In total, 93 (59.2%) patients fulfilled any of the criteria sets. Twelve (7.6%) patients fulfilled the mNY criteria; 68 (43.3%) patients fulfilled the ESSG criteria, 44 (28.0%) the Amor criteria and 60 (38.2%) the ASAS criteria for axial SpA (table 1). Eight of the 12 patients who fulfil the mNY criteria also fulfilled all the other criteria sets. The one patient only fulfilling the mNY criteria and no other criteria sets has ‘night pain’ as only SpA feature.

Conclusions: Approximately 60% of these patients fulfill at least one of the SpA criteria sets; 38% fulfil the ASAS axial SpA criteria. The selection criteria used in this cohort are easily applicable and work very well. Almost daily chronic back pain of short duration starting before the age of 45 years (in accordance with the entry criterion of ASAS axial SpA criteria) appears to be a very good, simple referral strategy at a rheumatology department, with a high yield of patients with SpA.

Classification criteria sets

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SECONDARY AMYLOIDOSIS IN ANKYLOSING SPONDYLITIS AND THE ROLE OF ANTI-TNF THERAPY

Objective: We evaluated the frequency of secondary amyloidosis, associated clinical features, and outcomes in ankylosing spondylitis (AS) patients diagnosed in the last decade.

Methods: The medical records of AS patients diagnosed at single academic medical center were reviewed for clinical evidence of amyloidosis. During routine follow-up, routine urinalysis was performed at each visit; patients with significant proteinuria underwent renal biopsy.

Results: We diagnosed 8 clinically apparent amyloidosis patients (1.1%) in our cohort of 730 AS patients (508M, 222F). Four patients undergoing hemodialysis were diagnosed secondary amyloidosis. Three patients had nephrotic syndrome and renal dysfunction and one patient had non-nephrotic proteinuria. When AS patients with amyloidosis were compared to AS controls, it was observed that the amyloidosis group was older, had longer disease duration, higher initial BASDAI scores and ESR values, and more frequent peripheral arthropathy (p<0.05). Logistic regression analysis revealed that the initial BASDAI level was an independent predictor for the development of secondary amyloidosis (OR:2.36). Six patients were administered anti-TNF therapy. The clinical findings resolved in these. In 2 patients with nephrotic syndrome and renal dysfunction, in addition to clinical improvement, there was decrement in proteinuria; renal function improved or remained stable.

Conclusions: Amyloidosis is not a rare occurrence in AS and may diagnosed after the development of end stage renal failure. Anti-TNF therapy is safe and effective in patients with renal failure, and at an earlier stage appears effective in improving renal function. The development of proteinuria in AS patients should occasion a search for underlying amyloidosis.
Poster Presentations

Eighth International Congress on Spondyloarthritis

P17 ROLE OF 25 HOXIVITAMIN D LEVELS IN ANKYLOSING SPONDYLITIS ACTIVITY AND DISABILITY

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Introduction: Few studies have researched the effects of vitamin D on Ankylosing Spondylitis (AS). There have been reports that patients with AS have low bone mineral density (BMD). In AS, inflammation appears to be a risk factor for low bone mineral density. Vitamin D reduces the production of inflammatory compounds that are part of the immune system. The aim of this work was to study the relationship between activity, disability, vitamin D levels and BMD in AS.

Material and Methods: Socio-demographic characterization included: gender, age, HLA-B27, body mass index (BMI), alcohol, coffee consumption and smoking habits. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and 25 hydroxy-vitamin D (25(OH)D3) levels were determined. Bath AS Disease Activity Index (BASDAI) was used to define disease activity and Bath AS Functional Index (BASFI) to determine function. BMD was evaluated in all patients. Correlation between continuous variables was calculated using Pearson’s coefficient.

Results: 43 patients were enrolled (12 women and 31 men), with a mean age of 49.1 years. Mean BASDAI was 4.4 cm and BASFI 3.7 cm. Laboratory findings revealed a mean ESR of 18, CRP of 1.1 mg/dl and 25(OH)D3 of 25.68, with 58.1% (25 patients) with low 25(OH)D3 levels. 13 patients were osteoporotic and 4 had osteopenia. There was no correlation between 25(OH)D3 levels and BASDAI (p=0.018) as well as with BASFI (p=0.052). No correlation was found between 25(OH)D3 levels and vertebral BMD (p=0.14), although a low/moderate positive correlation was found with BMD in femoral neck (p=0.31).

Discussion: Many authors believe that vitamin D deficiency may indirectly lead to osteoporosis and an increase in the inflammatory activity, but this study found neither that correlation, nor with functional impairment. The low/moderate correlation found between 25(OH)D3 levels and BMD in femoral neck and not with vertebral BMD, is probably due to the unreliability of spinal measurements, particularly in advanced disease with new bone formation in AS patients.

P18 THE PARADOXICAL EFFECTS OF TNF INHIBITORS ON BONE MINERAL DENSITY AND RADIOGRAPHIC PROGRESSION IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Objectives: To determine the longitudinal effects of TNF inhibitors on bone mineral density (BMD) and radiographic progression in patients with AS, and to assess independent factors associated with increased BMD in the lumbar spine.

Methods: Sixty-three patients with AS were included. Twenty-six patients were treated with TNF-inhibitors and 37 were not. BMD in the lumbar spine and right femur was measured by DXA at baseline, and at 1 and 2 year later. Lumbar spine radiography was performed at baseline and after 2 years. Radiographic progression was scored using the Stoke AS Spinal Score (SASSS) and the modified SASSS. Univariate and multivariate linear regression analyses were performed to determine factors independently associated with spinal BMD increases.

Results: BMD in the lumbar spine and total proximal femur of patients receiving TNF inhibitors increased consistently over 2 years compared with that in patients not receiving TNF inhibitors (p=0.001 and p=0.024), and treated patients showed significantly increased SASSS scores (p=0.046); however, syndesmophyte develop- ment was no different between the two groups. Changes in BMD and the number of new syndesmophytes in the lumbar spine correlated with 2-year changes in ESR only in patients receiving TNF inhibitors (p=0.019, p=0.036). TNF inhibitor ther- apy and the increase in SASSS were independently associated with the increased lumbar spine BMD (p=0.009 and p=0.001).

Conclusion: TNF inhibitors appear to be associated with increased SASSS scores and improvements in BMD. Further prospective studies with larger subject numbers are needed to validate this paradoxical role of TNF inhibitors.

P19 DEVELOPMENT OF A HEALTH INDEX FOR PATIENTS WITH ANKYLOSING SPONDYLITIS – FIRST STEPS OF A GLOBAL INITIATIVE BASED ON THE ICF GUIDED BY ASAS

1Herne, Germany; 2Leiden; 3Maartshuis, The Netherlands; 4Munich, Germany; 5Lucerne, Switzerland; 6Cleveland, USA; 7Alberta, Canada; 8Leeds, UK; 9Houston, USA; 10Otago, New Zealand; 11Swiss Paraplegic Research, Switzerland

Background: The burden of ankylosing spondylitis (AS) can be considerable. The influence of the disease on functioning, disability and health can be described with the International Classification of Functioning, Disability and Health (ICF) Core Set for AS. However, no ICF-based patient-reported outcome measure has been developed for AS patients.

Aim: To develop a measure to assess the overall impact of AS on health based on the ICF.

Method: Development is being performed in five phases: Preparatory - development of an item pool: 1st postal patient survey - Item reduction; Expert consulta- tion - Agreement on item reduction; 2nd postal patient survey - Validation of the draft version; Consensus Meeting - Agreement on a final version.

Results: An item pool was established which contains 251 items representing 44 categories. An international cross sectional study with 1915 AS patients (mean age 51.2±3.6, 53% male, BASDAI 5.5±2.4) was conducted in 4 continents. 82 items of the functioning part and 32 items of the environmental factors part showed good item properties. After selection by expert committee 50 functioning items and 16 environmental factor items have been tested in a 2 nd cross sectional survey. IRT will help to choose those items which represents the full spectrum of functioning. Discussion: In covering much of the ICF Core Set for AS, the items represent a whole range of abilities of patients with AS. After analysis of the 2 nd survey the draft version will be reduced to the final version. The final measure can be used in clinical trials as a new composite index that captures relevant information on the health status of the patients.

P20 DISEASE ACTIVITY AND NEW BONE FORMATION BOTH CONTRIBUTE TO FUNCTIONAL IMPAIRMENT IN ANKYLOSING SPONDYLITIS PATIENTS

Aguiar R., Ambrósio C., Cunha I., Barcelos A.
Dept. of Rheumatology, Hospital de Aveiro, Portugal

Introduction: Classically, the radiological damage was seen as the main responsible for the functional limitation in Ankylosing Spondylitis (AS) patients. More recent studies have suggested that both structural damage and inflammation contribute to impairment of spinal mobility. The aim of this work was to study the relationship between disease activity and new bone formation in AS patients.

Material and Methods: Socio-demographic characterization included: gender, age, duration of the disease and HLA-B27. Modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) was performed in all patients, as well as Ankylosing Spondylitis Quality of Life (ASQoL). Bath AS Disease Activity Index (BASDAI) was used to assess disease activity and Bath AS Functional Index (BASFI) to determine function. Correlation between continuous variables was calculated using Pearson’s coefficient.

Results: 37 patients were enrolled (11 women and 26 men), with mean age of 49.1
years and disease duration of 19.53 years. Mean mSASSS was 23.3 and ASQoL 3.75. Mean mSASSS was 23.3 and ASQoL 7.2. There was no correlation between age, gender and presence of HLA B27 with BASFI. A strong correlation was found between ASQoL and BASFI as well as between BASDAI and BASFI (p=0.78 and p=0.87, respectively). A low/moderate positive correlation was also found between BASFI and mSASSS (p=0.30) and between BASFI and disease duration (p=0.39).

Discussion: In this study, radiological damage had only a low/moderate correlation with BASFI. Disease activity, assessed with BASDAI, had a very strong correlation with functional impairment, probably because of the limitations caused by pain. Quality of life was compromised in patients with poor functional index.

P21

ORAL CONTRACEPTIVE PILL (OCP) USE IS ASSOCIATED WITH EARLIER ONSET OF DISEASE IN WOMEN WITH ANKYLOSING SPONDYLITIS

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Background: While AS is traditionally recognized as a predominantly male disease, the impact of gender on AS pathogenesis has not been established. The potential role of sex hormones in mediating gender impact on both AS susceptibility and disease severity remains unanswered.

Objectives: To elucidate the potential impact of exogenous estrogen on AS activity and severity. We hypothesize that exogenous estrogens, in the form of OCP, may result in a decrease in AS disease activity in premenopausal women.

Methods: The study population consists of premenopausal women with AS seen in a longitudinal clinic. The age of patients ranges from 18-50 yrs. Measures of disease severity include: use of biological agents, hip replacement surgery and BASFI scores as a surrogate marker of disability. A patient questionnaire was created and used to obtain information on patient demographics, past and present OCP use, menstrual history, pregnancy history, AS duration, medication use and hip replacement.

Results: Currently, a total of 93 study female participants have been enrolled from a longitudinal AS clinic. OCP users (n=77) and non-OCP users (n=16) were compared. OCP users were younger than non-OCP users (39.3 vs. 45.4, p=0.04) and were significantly younger at the onset of menarche (12.6 ± 14.4, p=0.01). Unexpectedly, OCP users had earlier onset of inflammatory back pain (21.9 vs 27.7, p=0.04). The diagnosis of AS was also made earlier in the OCP group (30.5 vs 36.8, p=0.05). There was no significant difference in anti-TNF or opioid use between the two groups, nor was there any difference in BASFI scores between OCP and non-OCP users.

Conclusions: The use of exogenous estrogens in the form of oral contraceptive pills is associated with a significantly earlier onset of back pain and earlier diagnosis of AS in women. While OCP use does not appear to impact disease severity, larger sample sizes are being addressed to address this issue.

P22

DIAGNOSTIC VALUE OF HIGH SENSITIVITY C-REACTIVE PROTEIN (hsCRP) FOR EARLY AXIAL SPONDYLOARTHRITIS (SpA): RESULTS FROM THE DESIR COHORT

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Introduction: CRP is part of the new ASAS classification criteria for axial SpA. hsCRP assays are more sensitive in detecting CRP at lower concentrations. hsCRP levels may be elevated in patients with axial SpA and hsCRP levels correlate better with CRP disease activity in axial SpA.

Aim: To compare the value of hsCRP versus CRP testing in diagnosing axial SpA.

Patients and Methods: Baseline data from 641 patients with inflammatory back pain (IBP) ≤3 years from the DESIR (Devenir des Spondylarthropathies Indifferenciees Recentes) cohort with no missing values for ASAS criteria was used. Design and inclusion criteria (age ≥18±30 years and inflammatory back pain ≥3 months≤3 years) have been previously reported. Baseline hsCRP was measured by immuno turbidimetric testing. Positive CRP and hsCRP were defined as levels ≥5mg/L and ≥2 mg/L, respectively.

Results: Patients included were 46.3% men, 58.2% HLA-B27 positive and on average 33.1 years old. Sixty nine percent (n=444) patients were classified as axial SpA and 204 without SpA (n=200). In patients with normal CRP, mean serum levels of hsCRP were higher in SpA (n=259) patients compared to no SpA (n=152) patients (1.7 vs 1.5 mg/L, p 0.03). Three percent of patients and 28% of controls had an elevated hsCRP. Forty-three out of 152 patients not classified as SpA had a negative CRP but positive hs-CRP. However, when substituting CRP by hs-CRP as one of the features in the ASAS criteria algorithm, none of these patients without SpA met ASAS criteria (figure 1).

Conclusions: We confirm that hsCRP is elevated in patients with axial SpA. Using the ASAS axial SpA criteria, hs-CRP instead of CRP did not increase the number of patients classified as axial SpA. Therefore, the role of hsCRP in diagnosis axial SpA seems limited.

Figure 1: ASAS criteria algorithm for axial SpA (HLA-B27 arm) comparing routinely CRP with hsCRP as one of the ASAS features.

P23

RELATIONSHIP BETWEEN DISEASE DURATION AND TREATMENT RESPONSE IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Background: A published report concluded that patients with ankylosing spondylitis (AS) with disease duration <10 years had a better response to anti-tumor necrosis factor (TNF) drugs in comparison to patients with disease duration >10 years.

Objective: To investigate the relationship between disease duration, baseline characteristics, and treatment responses in patients with AS.

Methods: Data pooled from 4 clinical trials (placebo [PBO] or sulfasalazine [SSZ] versus etanercept [ETN]) were analyzed in 4 disease duration categories and by age at diagnosis (≤40 or >40 years). Analyses were conducted using Chi-square tests and analysis of covariance models.

Results: 1281 patients were analyzed; baseline increasing age, decreasing age at diagnosis, and baseline increasing BASFI significantly correlated with increasing disease duration categories (p<0.05). A higher percent of patients responded to ETN compared with SSZ and PBO in all outcome measures and all disease duration categories. At week 12, patients with shorter disease duration had a tendency toward better response with ETN for most dichotomous outcomes, but not with SSZ or PBO. This trend was significant for ETN when analyzing patients aged ≤40 years at diagnosis. No significant differences were observed across disease duration categories for week 12 continuous outcomes (ASDAS, BASDAI, BASFI, etc.).

Conclusion: Regardless of the time from diagnosis, and thus treatment initiation, ETN was more effective in patients with active AS compared with SSZ and PBO. Patients treated with ETN with disease duration ≤2 years appeared to have the highest treatment response. Additional analyses are needed to further investigate the benefits of early treatment in AS.


P24

HOW FREQUENT IS FAMILY HISTORY IN SPONDYLITIS

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Introduction: Delayed diagnosis can be a severe problem with spondylitis. The ASAS group has developed new criteria for diagnosing “axial and peripheral Spond-
yarthritis”. In these criteria, presence in first-degree or second-degree relatives of Ankylosing Spondylitis (AS), psoriasis, uveitis, reactive arthritis and inflammatory bowel disease is of the upmost importance.

Objectives: The aim of this study is to verify how often family history features of spondyloarthropathies (SpA) are present in a cohort of patients with different SpA.

Material and Methods: During 3 months, all patients with SpA followed at our rheumatology department were included. Demographic and family history was collected from patient interviews.

Results: Ninety patients with SpA were enrolled [32 with AS, 43 with Psoriatic Arthritis (APs), 11 with Undifferentiated SpA and 4 with SpA associated to bowel disease. The mean age was 47 years with male predominance. Family history of psoriasis occurred in 44% of patients with PsA and 12.5% patient with AS. In contrast, family history of AS occurred only in patients with AS and 85.7% of them were HLA B27 positive. Anterior uveitis was the second most frequent family history feature in this cohort. In AS patients we found more first-degree relatives with family history of SpA, while in APs patients we equally found first and second-degree relatives. Most of the patients didn’t know the importance of family history to establish early diagnose.

Conclusions: Family history is a very important feature in early diagnosis of SpA. Family history features of SpA should be checked every time we suspect of a spondyarthritis.

P25

PREVALENCE OF CARDIOVASCULAR RISK FACTORS IN FILIPINOS WITH PSORIATIC ARTHRITIS

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Introduction: Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy affecting 1-9% of Asians with psoriasis. Patients have increased mortality mainly due to cardiovascular (CV) disease. Our aim is to determine the prevalence of CV risk factors among patients with PsA.

Methodology: We reviewed charts of patients diagnosed with PsA using the CASPAR criteria from 1999 to 2011 in 2 tertiary clinics. Demographic data, cardiovascular risk factors, and risk factor screening and management were extracted. Descriptive statistics as applied.

Results: Forty-one patients had PsA (73% females). Mean age at diagnosis of psoriasis and PsA were 39 and 43 years, respectively. Succeeding data were taken at latest consult, and denominators indicate available data as only around half of the patients had documented CV risk factors. Mean scores for inflammatory markers were HLA B27 positive. Anterior uveitis was the second most frequent family history feature in this cohort. In AS patients we found more first-degree relatives with family history of SpA, while in APs patients we equally found first and second-degree relatives. Most of the patients didn’t know the importance of family history to establish early diagnose.

Conclusions: Family history is a very important feature in early diagnosis of SpA. Family history features of SpA should be checked every time we suspect of a spondyarthritis.

P26

IMPAIRED HEART RATE RECOVERY INDEX IN PATIENTS WITH ANKYLOSING Spondylitis

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AIM: Ankylosing spondylitis (AS) is an inflammatory disorder that affects mainly young men and cardiac involvement which includes aortitis causing aortic regurgitation, myocarditis causing conduction disturbances, and increased myocardial fibrosis causing abnormalities of left ventricular relaxation and pericarditis is well known in AS. Heart rate recovery after exercise is a function of vagal reactivation, and its impairment is an independent prognostic indicator for cardiovascular and all-cause mortality. The aim of our study was to evaluate heart rate recovery index in patients with AS.

Patients and Methods: Fifty-one patients with AS (mean age 38.6±11.1 years, and mean disease duration 5.2±3.2 years, 30 male) and 50 healthy controls (mean age 40.4±10.3 years, 23 male) were included. Basal electrocardiography, echocardiography, and treadmill exercise testing were performed in all patients and controls. The heart rate recovery (HRR) index was defined as the reduction in heart rate from peak exercise to the rate at 1st (HRR 2), 2nd (HRR 3), and 3rd for the BASFI can reliably be imputed. The heart rate recovery (HRR) index was defined as the reduction in heart rate from peak exercise to the rate at 1st (HRR 2), 2nd (HRR 3), and 5th minute (HRR 4) after the cessation of exercise stress testing.

Results: There were significant differences in HRR 2, HRR 3, and HRR 4 indices between patients and controls (51.3±15.1 vs 65.2±14.0; p<0.001 and 61.0±14.2 vs 76.1±14.8; p<0.001). Effort capacity was markedly lower (8.1±2.0 vs 10.5±2.5 METs; p<0.001) in patients with AS compared to the controls.

Conclusion: The HRR index is deteriorated in patients with AS. These results may contribute to explain the mechanism of cardiac involvement in AS and attract attention to the importance of HRR index in the identification of high-risk patients.

P27

HOW TO DEAL WITH MISSING ITEMS IN BASDAI AND BASFI?

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Background: BASDAI and BASFI are commonly used instruments to monitor patients with AS, but it is not known to what extent missing items can be reliably imputed.

Objectives: To select the best strategy to substitute missing answers in the BASDAI and BASFI.

Methods: BASDAI and BASFI questionnaires from 12-years follow-up of the OA-SIS-study were used. The number of missing items per questionnaire was defined. Taking the fully completed questionnaires as reference, varying number of missing answers (1-4) were randomly generated. These missing answers were imputed by 5 strategies: worst, middle, lower or middle of the scales and middle or median of the remaining items of the questionnaire. Additionally, for the BASDAI, substitution of a missing item in one of the questions on morning stiffness by the remainder was assessed. Various levels of agreement (eg. absolute difference ≤0.7, SEM of reliability data) between imputed and original scores were defined as well as the percentage of patients that fulfilled these levels of agreement.

Results: BASDAI and BASFI showed few missing answers (52/171 and 56/171, respectively). The substitution of one of the BASDAI morning stiffness items by the other showed the best results, with an agreement of 99.7% for a difference in the total score ≤0.7. For the missing in the other questions from the BASDAI, substitution of the mean of the remaining items performed the best. In the BASDAI, substitution of one item resulted in an agreement of 93% for a difference in the total score ≤0.7. Assuming a same difference and imputation technique for the BASFI, an agreement of 99.5% was obtained for 1 missing item, 97.3% for 2 missing items and 92.7% for 3 missing items.

Conclusion: Substitution of the BASDAI and BASFI missing items by the remaining items of the missing item is the best strategy. Up to one missing item for the BASDAI and three for the BASFI can reliably be imputed.
SPINAL MOBILITY MEASURES ARE DEPENDENT ON AGE – THE MOBILITY STUDY

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Background: Spinal mobility is one of the core outcomes recommended by the ASAS for follow-up of patients with axial SpA. However, reference values for spinal mobility measures in healthy subjects are lacking and a possible age-effect is unknown.

Objectives: To assess the effect of age on spinal mobility measures among healthy people.

Methods: A cross-sectional study ("MOBILITY-study") was conducted among healthy volunteers aged 20-69 years old. Recruitment was stratified by gender, age (10-year categories) and height (10cm categories). Participants were any Caucasian volunteer. Exclusion criteria were factors potentially influencing spinal mobility (eg. back surgery). Several spinal mobility measures (including the BASMI) were investigated and they were compared across all age categories with ANOVA. The population was further divided according to the cutoff of 50 years old, as axial SpA rarely starts after the age of 50. The mean values were compared by independent sample t-test/Mann Whitney.

Results: A total of 393 volunteers were included, 51% males and with a mean age of 43.9 (SD 13.9) years. A significant decrease in all spinal mobility measures with increasing age was found, particularly between the older categories (50-59 and 60-69 years) and the younger categories (20-29 and 30-39). For instance, a mean cervical rotation of 79° (SD 9) was measured in the 20-29 category, 78° (SD 10) in the 30-39 category, 75° (SD 10) in the 40-49 category, 71° (SD 8) in the 50-59 category and 66° (SD 10) in the 60-69 category, with a significant difference between each of the first three and the last two categories. Dividing the population in two groups, significant differences in all the measures were found between the two age groups (eg. mean lateral spinal flexion 20.6cm (SD 3.2) for age<50 and 17.0cm (SD 3.3) if age≥50; p<0.001).

Conclusions: All spinal mobility measures significantly decrease with increasing age, which should be taken into account when assessing older patients.

INTERVERTEBRAL DISTANCE AND INTERNAL HIP ROTATION ARE DEPENDENT ON HEIGHT

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Background: Hip function in patients with ankylosing spondylitis can be measured with the intermalleolar distance (IMD) and with the internal hip rotation (IHR). The effect of age, height and gender on these measures is unknown.

Objectives: To assess the effect of height, age, gender and weight on IMD and IHR among healthy people.

Methods: A cross-sectional study was conducted among healthy volunteers aged 20-69 years old. Recruitment was stratified by gender, age (10-year categories) and height (10cm categories). IMD was measured with the participant supine, straight knees, legs separated as far as possible, measuring the distance between the medial malleoli. IHR was measured with the participant sitting with the knees and hips flexed 90°, knees together and the ankles moving apart as far as possible, measuring the distance between the medial malleoli. The effect of height, age, gender and weight was investigated through linear regression (unvariable followed by multivariable analysis). Interactions were tested.

Results: A total of 393 volunteers were included. IMD had a mean value of 112cm (SD 15) cm and IHR of 48cm (SD 10). Height (β 0.42, 95% CI 0.33;0.52) had a positive and age (β -0.44, 95% CI -0.53;0.52) a negative effect on IMD. Because of a significant interaction between age and gender on IHR was found, models were stratified for gender. In females, height (β 0.34, 95% CI 0.21;0.46) had a positive effect on IHR, whereas age (β -0.17, 95% CI -0.25;-0.09) and weight (β -0.12, 95% CI -0.22;-0.02) had negative effects. In males, height (β 0.50, 95% CI 0.37;0.63) and weight (β -0.14, 95% CI -0.24;0.04) had respectively a positive and negative effect on IHR.

Conclusions: IMD and IHR are both dependent on height and age; and IHR in addition also depends on gender and weight. Therefore these measures need age, gender and height adjusted reference values.

Reference:

DISEASE CHARACTERISTICS OF FILIPINO PATIENTS WITH ANKYLOSING SPONDYLITIS IN RHEUMATOLOGY CLINICS

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Introduction/Aim: Ankylosing spondylitis (AS) is a chronic arthritis that affects the spine, sacroiliac joints and on the occasion the big joints of the lower extremities of young individuals, with a slight male preponderance. In a descriptive study of 14 Filipino AS patients seen in a tertiary center, and the mean age at onset of symptoms was 21.8 years and the mean age at diagnosis was 29.7 years. This study aims to describe disease characteristics of Filipino patients diagnosed of AS seen in several Rheumatology clinics.

Materials and Methods: A retrospective study of case records of Filipino patients aged 18 years old and above seen in Rheumatology clinics. Aims to describe disease characteristics of young individuals, with a slight male preponderance. In a descriptive study of 14 Filipino AS patients seen in a tertiary center, and the mean age at onset of symptoms was 21.8 years and the mean age at diagnosis was 29.7 years. This study aims to describe disease characteristics of Filipino patients diagnosed of AS seen in several Rheumatology clinics.

Results: Forty-seven case records of Filipino patients with AS were reviewed in this study. The mean age was 33.2 at diagnosis and mean disease duration of 7 years. Male to female ratio is 46:1. The most common associated comorbidity was hypertension (27.6%). Seven cases (14.8%) of the study population have family history of AS and 25.5% have HLAB27 positivity. Most common manifestations were back pain (78.7%), peripheral joint involvement (70%) and neck pain (46.8%). Anterior uveitis was seen in 12.6%. Schober’s test was positive in 68% and common radiographic findings were sacroilitis and squaring of lumbar vertebra. Management of AS included use of nonsteroidal anti-inflammatory drugs (NSAIDS) as well as other options like methotrexate, sulfasalazine, cyclophosphamide and biologics.

Discussion: In this study, male predominance, family history of AS and HLA positivity was seen. Hypertension was found to be the most commonly associated comorbidity which may be secondary to use of NSAIDS.

Conclusion: We described the disease characteristics of Filipino patients with AS. These are consistent with those in literature with male predominance and back pain as the most common manifestation.

VALIDATION OF THE SELF-ADMINISTERED COMORBIDITY QUESTIONNAIRE IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Background: Comorbidities can importantly influence the results of clinical studies on functional outcomes. The generic self-administered comorbidity questionnaire (SCQ) is frequently used but has never been validated in ankylosing spondylitis (AS).

Objectives: To measure the agreement between SCQ-responses and medical records diagnosis, and to assess construct- and concurrent validity of the SCQ in AS.

Methods: Ninety-eight patients followed in the OASIS-study were included in the analysis. Data on the SCQ, disease activity (BASDAI, ASDAS-CRP), function (BASFI), health-related quality of life (HR-QoL; SF-36, ASQoL, EuroQol-VAS) were used. Agreement was calculated between the SCQ-items and comorbidities retrieved from medical records. Concurrent validity was assessed by the correlation of two other comorbidity indices: the Charlson-index and the Michaud/Wolfe index. Construct validity was assessed by the correlation of the SCQ with age, function, disease activity and overall HRQoL.

An adapted version of the SCQ was created after removing items on rheumatic diseases (osteoarthritis, back pain, chronic rheumatic disease) because they were conceptually overlapping with the index disease.

Results: The median SCQ-score was 5 (range 0-19) and the median adapted-SCQ-score was 2 (range 0-13). Agreement between self-report and medical records was moderate to perfect for all diseases included in the SCQ (kappa 0.47-1.00), except for stomach disease, depression, and osteoarthritis (kappa 0.14-0.15). The correlations of the SCQ with the Michaud/Wolfe index and the Charlson index were 0.39 and 0.24 respectively, and of the adapted-SCQ with both indices 0.53 and 0.36 respectively. The SCQ correlated weakly with age and disease activity, and moderately with function and HRQoL. The adapted-SCQ correlated weakly with age, and moderately with function and HRQoL.

Conclusion: The SCQ can be used to measure comorbidities which have impact on functional outcomes in AS, but the rheumatic items showed low agreement. Exclusion of these items improved construct and concurrent validity.
P32
ACHIEVING ASDAS-CRP MAJOR IMPROVEMENT AND INACTIVE DISEASE IN PATIENTS WITH ANKYLOSING SPONDYLITIS TREATED WITH GOLIMUMAB IS ASSOCIATED WITH NORMALIZED HEALTH RELATED QUALITY OF LIFE: TWO-YEAR RESULTS FROM THE GO-RAISE TRIAL

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Background: Significantly greater improvements in health-related quality of life (HRQoL) and reduction of impact of disease on work productivity were observed in patients (pts) with ankylosing spondylitis (AS) treated with golimumab when compared with placebo at weeks 14 and 24.

Objective: This analysis examined association of ASDAS major improvement and inactive disease with these improvements and the maintenance over two years.

Methods: In the GO-RAISE study, 350 pts with definite AS according to the modified NY criteria were randomly assigned in a 1.8:1.8:1 ratio to receive subcutaneous golimumab (40 mg: 75 mg: placebo) every 4 weeks. The primary endpoint was an improvement in ASDAS-CRP of ≥2.1 and ≤-2.2. The secondary endpoints were an improvement of ≥2.7 in ASDAS-PCR and mobility (SpA). The investigations of others markers are necessary to better assess the subclinical atherosclerosis and metabolic syndrome (MS) in patients with ankylosing spondylitis (AS) is unknown, although cardiovascular (CV) mortality 1.5 times higher than the general population.

Results: At weeks 14 and 24 the combined golimumab groups had greater median improvements in ASDAS scores compared with placebo (1.6 vs. 0.4 and 1.7 vs. 0.3, respectively, p<0.001 for both). At weeks 52 and 104, when all pts received golimumab, all groups had comparable improvements in ASDAS, ranging from 1.9 to 1.7. At weeks 52, 104, 39.9% and 41.6% achieved ASDAS inactive disease and week 52 and 104. Pts with major improvement for these time points were 49.1% and 52.9%. For pts achieving ASDAS inactive disease at weeks 52 and 104, 57.1% and 65.5%, respectively, had FCS ≥50. Inactive disease pts had 64.8% and 74.1% with PCS ≥50 and 62.1% and 65.3% with MCS ≥50 for these time points. Improvements in productivity were greater for pts with ASDAS inactive disease compared with non-inactive disease at weeks 52 and 104 (5.8 vs. 2.9 and 5.8 vs. 3.1, p<0.001 for both). Similar results were achieved for ASDAS responders compared with non-responders (5.4 vs. 2.4 and 5.8 vs. 2.6, p<0.001 for both). Baseline 40 pts were unreimbаемое because of AS. At week 52, 6 of the 16 (37.5%) pts who achieved inactive disease regained employability, while 11 of the 16 (73.3%) pts who had major improvement regained employability. At week 104, 7 of the 18 (38.9%) pts who achieved inactive disease regained employability, while 13 of the 18 (72.2%) pts who had major improvement regained employability.

Conclusion: Achieving ASDAS inactive disease or major improvement in pts with AS after treatment with golimumab is associated with improvements in HRQoL and productivity. A trend towards regaining employability was observed for pts with clinical improvements, but this association would need to be substantiated in larger studies.

P33
THE HEART IN ANKYLOSING SPONDYLITIS STUDY (HAS STUDY)

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Introduction: Heart disease is one of the extra-articular manifestations of ankylosing spondylitis (AS) and may affect the three compartments of the heart and the great vessels. Early detection of cardiac dysfunction can minimize the impact of cardiovascular disease on mortality in patients with AS.

Aims: Evaluate the frequency of myocardial damage in patients with AS by magnetic resonance imaging (CMRI).

Patients and Methods: 33 patients with AS (modified New York Criteria, 1984), and 30 healthy controls (HC) matched for age, sex, BMI, and criteria for metabolic syndrome were included. Diabetics and patients with previous coronary disease or other chronic inflammatory diseases were excluded. The presence of edema, myocardial fibrosis, as well as the resting perfusion and other morphological and functional aspects were evaluated by CMRI.

Results: The duration of disease and diagnosis were 16.5±9.4 years and 10.7±6.8 years, respectively. The patients had moderated disease activity (BASDAI = 2±2.1 and ASDAS-PCR = 2±1.2), with impaired function (BASFI = 3.8±2.7) and mobility (BASMI = 4.1±2). Just over 50% of the patients were using TNF blockers for at least six months. Although not statistically significant, patients with AS showed relevant differences in the CMRI: two with myocardial edema (p<0.049) and five with mild aortic regurgitation (p<0.02). Similarly, ectasia of the aortic arch was twice more frequent in patients with AS (n=8) than in HC (n=4) but not significant (p=0.27). Moreover, one patient had extensive miocardial edema, suggesting myocardiitis but asymptomatic.

Conclusion: Our results suggest that patients with AS long evolution did not show greater myocardial impairment than healthy controls. Other markers of cardiac involvement should be better studied in order to explain the higher cardiovascular mortality observed.

P34
TRADITIONAL RISK FACTORS FOR SUBCLINICAL ATHEROSCLEROSIS CANNOT EXPLAIN THE HIGHER PREVALENCE OF CARDIOVASCULAR DISEASE IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Introduction: Recently studies have shown increased cardiovascular risk in several chronic inflammatory rheumatic diseases such as systemic lupus erythematosus and rheumatoid arthritis. However, the role of inflammation, subclinical atherosclerosis and metabolic syndrome (MS) in patients with ankylosing spondylitis (AS) is unknown, although cardiovascular (CV) mortality 1.5 times higher than the general population.

Aims: Study the traditional risk factors and parameters of subclinical assessment in patients with AS.

Patients and Methods: 50 patients with AS (modified New York Criteria, 1984) and 35 healthy controls matched for age, sex, BMI, smoking and MS were included. Individuals with diabetes mellitus, previous coronary disease, using statins or other chronic inflammatory diseases were excluded. The midintimal thickness (IMT), the diameter and the distension of the artery were measured by carotid ultrasound (echo-tracking method). The thickening of the aorta was assessed by pulse wave velocity (PWV) (Complior device, France).

Results: The duration of the disease and the diagnosis were 17.5±9.7 years and 10.2±6.3 years, respectively. The patients had moderate activity (BASDAI = 2±2.2 and ASDAS-PCR = 2±1.3), with impaired function (BASFI = 3±9.2±6.3) and mobility (BASMI = 4±6.2±2). Just over 50% of the patients were using TNF blockers for at least six months. None of the parameters of endothelial function was different between patients and controls [PWV (p=0.18), IMT (p=0.8), diameter (p=0.13) and carotid distension (p=0.16)]. Likewise, the lipid profile was similar between groups.

Conclusion: Our results show that the traditional risk factors for atherosclerosis do not seem to explain the higher cardiovascular mortality in patients with AS. The investigations of others markers is necessary to better assess the subclinical atherosclerosis in order to minimize the impact of CV disease on mortality in this scenario.

P35
THE PERFORMANCE OF PSORIATIC ARTHRITIS CLASSIFICATION CRITERIA IN PSORIATIC ARTHRITIS IN TURKISH PATIENTS

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Objectives: Psoriatic arthritis (PsA) is chronic inflammatory disorder of peripheral joints, spine and entheses. It is a member of the spondyloarthropathies (SpA). The
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ANTI-CYClical CITRULLINATED PEPTIDE ANTiBODIES AND SHARED-EpIToPE PREVALENCE IN PsORiATiC ARTHRiTIS

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Background: Low number of patients with Psoriatic Arthritis (PaA) expressed antibodies to cyclic citrullinated peptide (anti-CCP). Patients who suffer PaA, more in polyarticular subset, expresses shared-epitope like Rheumatoid Arthritis (RA), but is unknown these feature relation with anti-CCP prevalence in PaA patients.

Objectives: Establish the presence and clinical significance of anti-CCP, and shared-epitope in PaA.

Methods: We reviewed 108 patients with PaA according to criteria of Moll and Wright. Anti-CCP determined by third generation ELISA, HLA DR by low sensitivity PCR. Gender and clinical subset (polyarthritics, oligoarthritis, distal interphalangeal limited, arthritis “mutilans”) and axial were recorded.

Results: b/108 (5.6%) were anti-CCP positive. 2 (3.3%) were males and 4 (66.6%) females, without differences in sex distribution in front anti-CCP negative. Clinical subsets in anti-CCP positive patients were 3 patients (50%) oligoarthritis and 3 (50%) polyarticular. 5 patients fulfilled ARA criteria to RA, but one of them have typical PaA radiological findings, and only other two might be RA classified. 4/6 (66.7%) anti-CCP positive patients expressed shared-epitope in front 42/102 (43.4%) CCP negative, but difference isn’t significant. We found shared-epitope expression differences related with clinical PaA subsets or gender.

Conclusions: Shared-epitope presence 40% of patients with PaA expressed shared-epitope however anti-CCP prevalence is very low. Shared-epitope isn’t related with any PaA clinical subset.

We failed to associate anti-CCP positive with gender or PaA clinical subset.

We failed in associate expression of shared-epitope with gender or PaA clinical subset.

The lower prevalence of anti-CCP positive with shared-epitope and patients who fulfilled ARA criteria to Rheumatoid arthritis, only 2 (1.85%), is an indirect remark of the high specificity of Wright and Moll criteria.

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SECUKINUMAB IMPROVES SIGNS AND SYMPTOMS OF PsORiATiC ARTHRiTIS: A 24-WEeEK, DOuBLE-BLiiN, TRIAL

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Objectives: This study assessed the efficacy and safety of secukinumab for the treatment of psoriatic arthritis (PsA).

Methods: 42 patients with active PaA who fulfilled CASPAR criteria were randomized 2:1 to receive two injections of secukinumab (10mg/kg) or placebo, given 3 weeks apart. The primary efficacy endpoint was the proportion of ACR20 responders at Week 6 in active versus placebo (one-sided p<0.01).

Results: 35 (83.3%) patients (25 on secukinumab, 10 on placebo) completed the study. Baseline characteristics were balanced between groups including parameters.

Co-existing psoriasis, prior TNFi exposure and co-medication with DMARDS were present in 23, 11 and 21 patients on secukinumab and in 11, 5 and 10 on placebo, respectively. ACR20 responders on secukinumab vs. placebo were 39% vs. 23% (p<0.07) at Week 6, 39% vs. 15% at Week 12, 43% vs. 18% at Week 24, ACR50 responders at Week 6 in secukinumab vs. placebo were 13% vs. 3% (p<0.01), respectively. At Week 6, CRP reductions at Week 6 were greater on secukinumab (median [range] at baseline vs. Week 6: 4.9 [0.3, 43.0] vs. 3.0 [0.2, 15.2]) than on placebo (6.2 [1.3, 39.7] vs. 5.0 [0.8, 29.6]). Overall rate of adverse events (AEs) was comparable in secukinumab 26 (93%) vs. placebo 11 (79%). Infections were reported in 16 (57%) patients on secukinumab and 7 (50%) on placebo.

Conclusions: Although the primary endpoint was not met, patients showed rapid and sustained improvements of clinical scores and CRP levels up to Week 28. The safety profile of secukinumab was favorable. These findings warrant further larger phase III clinical trials in PaA.

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THE FREQUENCY OF NON-RADIOGRAPHIC AXIAL SPONDYLOARTHITIS IN RELATION TO SYMPTOM DURATION IN PATIENTS REFERRED BECAUSE OF CHRONIC BACK PAIN

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Aim: This study was aimed at investigating of the frequencies of non-radiographic axial SpA (nr-axSpA) and ankylosing spondylitis (AS) diagnoses and their ratios
in relation to symptom duration in patients referred because of chronic back pain and suspicion of axial SpA.

Material and Methods: In this monocenter study performed in Berlin orthopaedists and primary care physicians were solicited to refer patients with chronic low back pain (duration >3 months) and onset of back pain before <45 years of age to a SpA-specialized rheumatology outpatient clinic for further diagnostic investigation if at least one of the following screening parameters was present: 1) inflammatory back pain, 2) positive HLA-B27, and 3) sacroiliitis detected by imaging. The final diagnosis was made according to the opinion of rheumatologists. The ratio of nr-axSpA to AS was analysed in relation to the duration of symptoms.

Results: A diagnosis of definite axial SpA was made in 43.7% of the referred patients (n = 552). Axial SpA was diagnosed in a similar percentage of about 50% if back pain duration was >9 years but decreased to 36% if symptom duration was >9 years. Nr-axSpA represented the majority of patient (67.3%) only if duration of back pain was 1 year and less at the time of referral. Between 1 and 6 years of back pain duration the probability of nr-axSpA and AS was nearly equal (1-3 years: 52.5% and 47.5%, respectively; 3-6 years: 53.7% and 46.3%, respectively). In patients with back pain duration of 6-9 years, AS was more likely (61.1%) to be diagnosed than nr-axSpA (38.9%), and this increased further over time.

Conclusion: Non-radiographic axial SpA is a relevant diagnosis in patients with axial SpA at any time point; however, the probability of non-radiographic form of axial SpA is highest if symptom duration is short.

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PREVALENCE AND RISK FACTORS OF ANTERIOR ATLANTOAXIAL SUBLUXATION IN ANKYLOSING SPONDYLITIS

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Objective: In AS, cervical spine is also vulnerable the disease process in addition to other spines and sacroiliac joints. But atlantoaxial subluxation (AAS) has been considered as uncommon feature despite of several case reports in AS, unlike rheumatoid arthritis (RA). This study aims at assessing the prevalence and risk factors of AAS in AS patients.

Methods: Consecutively, total 819 AS patients who fulfilled the modified New York criteria and examined with full-flexion lateral view of cervical spine x-ray, were enrolled from the outpatient clinic of Hanyang University Hospital for Rheumatic Diseases in Korea. The patients were retrospectively reviewed medical records and prospectively investigated anterior atlanto-dental interval (AADI) in lateral flexion view of C-spine x-ray by two experienced musculoskeletal radiologists. In this study, we defined the AAS as AADI of greater than 3 mm, and the significant progression of AADI as greater than 0.5mm/yr in progression rate.

Results: The AAS was revealed in 12.5% (102/819 patients), simultaneously in 32.3% (33/102 patients) at time of AS diagnosis. Significant progression of AADI was in 22.1% (17/77 patients) of positive, while 5.9% (19/324 patients) of negative AAS (p-value=0.000). As multivariate logistic regression analysis, the development of AAS was significantly associated with duration of AS duration (OR 1.075, p-value 0.002, 95% CI 1.027-1.126), and peripheral arthritis (OR 1.963, p-value 0.000, 95% CI 1.833-2.108). After three months diagnosed a AAS, 15.9% of the patients did improve APR in performance-based, but not in self-reported physical function (BASFI). Besides, a combination of performance-based tests and BASFI-questionnaire could have additional value in future evaluations of physical function for patients receiving anti-TNF therapy.

Conclusion: A prospective study was conducted in order to establish whether performance-based tests of physical function have additional value in evaluating physical function in AS patients after three months of anti-TNF therapy. A combination of performance-based test and BASFI-questionnaire could have additional value in future evaluations of physical function for patients receiving anti-TNF therapy.

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PRESENCE OF PERIPHERAL ARTHRITIS PREVENTS RADIOGRAPHIC SPINAL DAMAGE PROGRESSION IN ANKYLOSING SPONDYLITIS: OBSERVATION STUDY OF KOREAN SPONDYLOARTHRITIS REGISTRY (OSKAR) CROSS-SECTIONAL AND RETROSPECTIVE COHORT STUDY OVER 5 YEARS

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Objective: To determine whether presence of peripheral arthritis can affect the progression of structural damage in patients with ankylosing spondylitis (AS).

Methods: A total of 915 patients with AS from the Observation Study of Korean Spondyloarthropathy Registry (OSKAR) cohort were enrolled for this analysis. We used a two-step approach to explore the relationships between the peripheral arthritis and the progression of spinal structural damage in AS. First, all OSKAR data were analyzed in relation to the history of peripheral arthritis on cross-sectional survey. Second, we retrospectively analyzed the radiographic spinal progression for 5 years according to the presence or absence of peripheral arthritis. The modified Stoke AS Spinal Score (mSASSS) were examined by two experienced radiologists to validate the results. The collection of the clinical parameters was conducted to investigate the associations between clinical factors and the radiographic progression.

Results: The agreement between the two readers regarding mSASSS was very good: ICC coefficient 0.75 (95% CI 0.61-0.82) and 0.71 (95% CI 0.58-0.82) at each time. On cross-sectional survey, in spite of adjusting for multiple comparisons by Bonferroni correction, the patients with history of peripheral arthritis had fewer mSASSS unit than those without history of peripheral arthritis (19.56±10.6 vs 22.67±0.81, p=0.005). In a retrospective analysis over 5 years, the mean progression of mSASSS in patients with peripheral arthritis was 3.26±0.58 units, while that of mSASSS in patients without peripheral arthritis was 4.97±0.44 units (p=0.024).

Conclusion: The patients with the peripheral arthritis had slower radiographic spinal damage progression than those without peripheral arthritis.

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WHAT DO WE MISS? ASAS NON-RESPONDERS ON ANTI-TNF THERAPY SHOW IMPROVEMENT IN PHYSICAL FUNCTION

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Aim: A prospective study was conducted in order to establish whether performance-based tests of physical function have additional value in evaluating physical function in AS patients after three months of anti-TNF therapy. A combination of performance-based test and BASFI-questionnaire could have additional value in future evaluations of physical function for patients receiving anti-TNF therapy.

Patients and Methods: AS patients (n=82) completed seven performance-based tests, before and three months after the start of anti-TNF therapy. The time needed to complete the performance-based test was measured. A ≥20% intra-individual improvement on the performance-based tests was used to classify patients as “improver” or “non-improver” in performance-based physical function. Patients were also defined as “improver” or “non-improver” on self-reported physical function (BASFI) and as “responder” or “non-responder” to anti-TNF therapy on ASAS20 improvement criteria. The agreement between improvement on performance-based physical function and (i) improvement on self-reported physical function and (ii) response on the ASAS20 criterion was assessed. Cross-tabulations were produced. After three months in a TNF therapy, 20.7% of the patients improved in performance-based, but not in self-reported physical function (BASFI). Besides, 15.9% of the patients did improve ≥20% in performance-based physical function, but was not responding to anti-TNF therapy according to the ASAS20 improvement criteria.

Conclusion: Performance-based tests provide the opportunity to generate additional information in the evaluation of physical function after anti-TNF therapy. A combination of performance-based test and BASFI-questionnaire could have additional value in future evaluations of physical function for patients receiving anti-TNF therapy.

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THREE EASY TO PERFORM TESTS OF PHYSICAL FUNCTION SHOW IMPROVEMENT IN ASAS NON-RESPONDERS AFTER 3 MONTHS OF ANTI-TNF THERAPY IN ANKYLOSING SPONDYLITIS

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Aim: To determine whether presence of peripheral arthritis can affect the progression of structural damage in patients with ankylosing spondylitis (AS).

Methods: A total of 915 patients with AS from the Observation Study of Korean Spondyloarthropathy Registry (OSKAR) cohort were enrolled for this analysis. We used a two-step approach to explore the relationships between the peripheral arthritis and the progression of spinal structural damage in AS. First, all OSKAR data were analyzed in relation to the history of peripheral arthritis on cross-sectional survey. Second, we retrospectively analyzed the radiographic spinal progression for 5 years according to the presence or absence of peripheral arthritis. The modified Stoke AS Spinal Score (mSASSS) were examined by two experienced radiologists to validate the results. The collection of the clinical parameters was conducted to investigate the associations between clinical factors and the radiographic progression.

Results: The agreement between the two readers regarding mSASSS was very good: ICC coefficient 0.75 (95% CI 0.61-0.82) and 0.71 (95% CI 0.58-0.82) at each time. On cross-sectional survey, in spite of adjusting for multiple comparisons by Bonferroni correction, the patients with history of peripheral arthritis had fewer mSASSS unit than those without history of peripheral arthritis (19.56±10.6 vs 22.67±0.81, p=0.005). In a retrospective analysis over 5 years, the mean progression of mSASSS in patients with peripheral arthritis was 3.26±0.58 units, while that of mSASSS in patients without peripheral arthritis was 4.97±0.44 units (p=0.024).

Conclusion: The patients with the peripheral arthritis had slower radiographic spinal damage progression than those without peripheral arthritis.
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**BASFI IS A BETTER INDICATOR OF LOW QUALITY OF LIFE THAN BASDAI IN ANKYLOSING Spondylitis – RESULTS FROM THE SCOTLAND AND IRELAND REGISTRY FOR ANKYLosing SPONDYLITIS (SIRAS)**

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**Introduction:** BASDAI and BASFI are used to determine disease activity and function amongst Ankylosing Spondylitis (AS) patients, although the relationship between both, and quality of life (QoL), is not well established. The aim of this study was to investigate this relationship in the context of other QoL markers.

**Methods:** SIRAS collects data on clinically diagnosed AS patients in Scotland. BASDAI, BASFI and other clinical markers are obtained from medical records, and postal questionnaires provide patient-reported data, including QoL. The study was to investigate this relationship in the context of other QoL markers.

**Results:** 311 patients had complete BASDAI, BASFI and QoL data (75% male; median age 51yrs; median ASQoL: 6.0, inter-quartile range: 1-11). Low QoL was associated with high disease activity (BASDAI ad: risk ratio: 3.7; 95%CI 2.3-6.0) and poor function (BASFI: 4.1; 3.4-10.9). However, after mutual adjustment, only poor function remained an independent predictor of low QoL (4.8; 2.4-9.6). The relationship with disease activity was greatly attenuated and no longer significant (0.8; 2.4). Other factors independently associated with low QoL were: female gender (1.6; 1.1-2.4), chronic widespread pain (2.7; 1.5-4.8), fatigue (1.8; 1.2-2.8), ever receiving anti-TNF therapy (1.5; 1.0-2.2), and social deprivation (2.0; 1.1-3.5). No other clinical measures (inflammation measured by CRP or ESR, peripheral joint involvement, or co-morbid disease) were independently associated with low QoL.

**Conclusions:** Integral to anti-TNF prescribing guidelines in the UK, BASDAI is considered as the important clinical indicator in AS. However, clinicians should be aware that BASFI is a stronger predictor of low QoL. Patients with a high BASFI were almost five times more likely to report low QoL than other patients. In addition, after adjusting for BASFI, QoL was predicted by no other clinical variables.

**Sponsors:** Abbott Laboratories and Pfizer Inc.

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**PREVALENCE OF INFLAMMATORY BACK PAIN IN A UK PRIMARY CARE POPULATION**

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**Introduction:** Inflammatory back pain (IBP) is the earliest and commonest symptom of axial spondyloarthritis (SpA). SpA can be difficult to diagnose in the early stages, but identifying patients with IBP may offer a way to reduce diagnostic delay. As part of a study to determine the prevalence of SpA in the UK we examined the prevalence of IBP in a UK primary care population.

**Patients and Methods:** The study took place in a large general practice in Norfolk, UK. Potential participants aged 18-80 years were identified from their primary care records as having consulted on at least one occasion with low back pain. A self-completed screening questionnaire was sent to a random sample of 978 patients asking about IBP symptoms.

**Results:** Five hundred and five completed questionnaires were returned (response rate 51.6%). Respondents had a median age of 60 years (IQR 48-67) and 44.8% were male. Eighty percent reported back pain of at least 3 months duration. The ASAS IBP criteria were fulfilled by 75 (14.9%) respondents, the Calin criteria by 132 (26.1%) and the Berlin criteria by 151 (29.9%). IBP was seen more commonly in women, but this difference was not statistically significant. The prevalence of IBP among patients with at least one previous consultation for back pain was 7.7% (95% CI 6.2, 9.5%) using the ASAS criteria, 13.5% (11.5, 15.8) using the Calin criteria and 15.4% (13.3, 17.8) using the Berlin criteria.

**Discussion:** Estimations of the prevalence of IBP are affected by the criteria chosen for classification. This should be considered when comparing studies, and when assessing patients in the clinical setting.

**Sponsors:** Abbott Laboratories and Pfizer Inc.

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**DISEASE PATTERNS OF PSORIATIC ARTHRITIS IN A LARGE SERIES OF BRAZILIAN PATIENTS WITH SPONDYLOARTHRITIS**


**Brazilian Registry of Spondyloarthritis (RBE)**

**Aim:** To analyze disease patterns in a large cohort of Brazilian patients with psoriatic arthritis.

**Patients and Methods:** A common protocol of investigation was applied to 1505 patients with spondyloarthritis (SpA) distributed in 29 reference centers in Brazil. Clinical and demographic variables, associated to disease indexes (BASDAI, BASFI, BASRI, MASES, ASQoL), were investigated. Psoriatic arthritis was present in 271 patients (18.4%); 206 patients (13.7%) presented predominant peripheral disease and 65 patients (4.3%) predominant axial disease.

**Results:** Patients with psoriatic arthritis were older (p<0.001) and had shorter disease duration (p<0.001). Psoriatic arthritis was positively associated to female gender (p<0.001), Caucasian race (p<0.001), upper limb arthritis (p<0.001), lower limb arthritis (p<0.001), dactylitis (p<0.001), positive family history (p=0.016), heart (p=0.033) involvement, and use of methotrexate (p<0.001). Painful (p<0.001) and swollen (p<0.001) joints were also more frequent in patients with psoriatic arthritis. There was negative association among psoriatic arthritis and low back pain (p<0.001), buttock pain (p=0.001), cervical pain (p=0.038), hip involvement (p<0.001), radiologic sacroiliitis (p<0.001), uveitis (p<0.001), positive HLA-B27 (p=0.001), and use of NSAIDs (p=0.001) and sulfasalazine (p<0.001). MASES, BASDAI, and ASQoL presented similar indices in the two groups, but BASRI (p<0.001) and BASFI (p=0.01) presented lowered values in patients with psoriatic arthritis.

**Conclusion:** In this large and heterogeneous cohort of Brazilian patients, psoriatic arthritis was significantly associated with peripheral involvement.

**Sponsors:** Abbott Laboratories and Pfizer Inc.
**Objective:** These comorbidities in AS vary substantially. They have substantial influence on health outcomes. However, data on the prevalence of arthritis (SpA), are common in patients with ankylosing spondylitis (AS) and may vary between two groups: age at onset <16 years (JSpA group) and age at onset ≥16 years (adult-onset SpA group).

**Results:** Among the 1424 patients, 235 presented disease onset before 16 years (16.5%). Patients with JSpA were predominantly male (86.0%) and white (61.7%), with mixed (axial + peripheral) clinical presentation (53.8%) and positive HLA-B27 (79.6%). The clinical and epidemiological variables associated with JSpA were male gender (p<0.001), lower limb arthritis (p=0.001), enthesitis (p=0.008), anterior uveitis (p=0.041) and positive HLA-B27 (p=0.017), associated to lower scores of disease activity (BASDAI; p=0.007) and functionality (BASFI; p=0.036), and higher radiographic scores (BASRI total, p<0.001; and BASRI Hip, p=0.001). Pure peripheral involvement (p=0.001), cutaneous psoriasis (p=0.001), inflammatory bowel disease (p=0.023), dactylitis (p=0.024) and nail involvement (p=0.004) were more frequent in patients with adult-onset SpA.

**Conclusions:** Patients with JSpA in this large Brazilian cohort affected predominantly male gender and presented a mixed (axial + peripheral) clinical presentation associated to HLA-B27 positive and worse radiographic scores.

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**CASPAR AND MODIFIED CASPAR CRITERIA IN EARLY PSA PATIENTS**

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**Objective:** To evaluate and validate CASPAR and Modified CASPAR criteria for psoriatic arthritis (PsA) in early PsA and early RA pts (disease duration less than two years).

**Patients and Methods:** CASPAR (1) and Modified CASPAR (2) criteria difference: if psoriasis is not present at the current examination, but documented previously, in medical records signed by rheumatologist or dermatologist, CASPAR would score one point, and modified CASPAR would score two, the same as for the current psoriasis. 62 pts with early PsA and 54 pts with early RA were involved. Clinical diagnosis (consensus of the two rheumatologists) of PsA was accepted as the gold standard. The Caspar and Modified Caspar criteria were applied to all patients. Sensitivity was calculated as percentage of PsA patients who satisfied, and specificity as percentage of RA patients who did not satisfy the investigated criteria sets.

**Results:** The sensitivity for the CASPAR criteria was 88.7% and for the Modified CASPAR 91.9%. The CASPAR criteria were mostly met on the basis of current psoriasis (85.5%), negative test for RF (91.9%) and evidence of dactylitis (54.9%). Two patients with psoriasis documented in personal history, but not seen at the current examination, met modified Caspar, but not the CASPAR criteria. Two patients with PsA sine psoriasis met both criteria sets. Specificity for both Caspar and Modified Caspar was 98.1%.

**Conclusion:** Using the same scoring system for the current and previous psoriasis documentation by rheumatologist or dermatologist, Modified CASPAR criteria demonstrated slightly higher sensitivity than CASPAR criteria. Specificity did not differ between Caspar and Modified Caspar.

**References:**

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**PREVALENCE OF SPA-RELATED COMORBIDITIES, OSTEO-POROSIS AND FRACTURES IN ANKYLOSING SPONDYLITIS**

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**Background:** Comorbidities, both related and unrelated to the concept of spondyloarthropathy (SpA), are common in patients with ankylosing spondylitis (AS) and may have substantial influence on health outcomes. However, data on the prevalence of these comorbidities in AS vary substantially.

**Objective:** To review the literature on the prevalence of uveitis, psoriasis, inflammatory bowel disease (IBD), osteoporosis and vertebral fractures in patients with AS.

**Methods:** Medline, Embase and Cochrane were searched systematically up to November 2011, supplemented by hand search of references. Articles were eligible if reporting original data on the prevalence of one of the above mentioned comorbidities. Demographic and prevalence data were extracted and studies were combined to express prevalence with 95% confidence intervals (CI) weighted for the number of patients included in the studies.

**Results:** Out of 7817 studies initially retrieved, 188 met the inclusion criteria and 13 studies were added by hand search. The prevalence of uveitis, psoriasis, IBD, osteoporosis and vertebral fractures could be calculated in respectively 137 (40141 patients), 53 (25695 patients), 66 (30410 patients), 24 (2786 patients), and 17 (2285 patients) articles. The overall mean age was 43.9 (SD 6.9) years, mean disease duration 16.7 (SD 6.2) years and 63.7% were men. The weighted mean prevalence of uveitis was 30.3% (95% CI 30.2;30.4) but increased with longer disease duration. Prevalence of psoriasis was 11.3% (95% CI 11.2-11.4) but increased with longer disease duration. Prevalence of osteoporosis was 20.5% (19.4;21.6) in the lumbar spine and 20.9% (95% CI 10.4-11.4) at the femoral neck in studies specifically screening for radiological evidence, and 3.4% in one study based on medical records. Vertebral fractures were present on 21.8% (95% CI 21.0-22.4) of radiographs specifically screening for this and 5.8% by self-report (only one study).

**Conclusion:** SpA-related comorbidities, osteoporosis and vertebral fractures are common in patients with AS but may vary with disease duration and method of investigation. Attention for comorbidities in relation to outcome in AS is recommended.
psychological status and mediation respectively. Data were analyzed by the SPSS 17.0 software.

Results: Anxiety was found in 25.5% of our patients. SAS scores were significantly higher than control group, but no statistical difference was found with depression. Morning stiffness, BASDAI, BASFI, nocturnal pain, total back pain, change control, resignation coping, SAS and SDS scores of parents were positively correlated with SAS and SDS scores of AS adolescents respectively. In the hierarchical multivariate analysis of all psychological variables contributed significantly to the variance in BASFI scores, adding an additional 15.7% to the overall R-square beyond that accounted by demographic and medical variables (R-square 29%), resulting in a final R-square of 44.7%. Depression, internality and resignation coping style accounted for a significant portion of the variance in BASFI scores in the final model.

Conclusions: The prevalence of anxiety and depression in adolescents with AS is obviously increased. Psychological variables accounted for significant variability in functional limitation beyond demographic and clinical variables in these patients. Attention should be paid to psychological factors in the comprehensive management of AS adolescents.

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EFFECTS OF SLEEP QUALITY TO NOCTURNAL PAIN IN PATIENTS WITH ANKYLOSING SPONDYLITIS
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Introduction: The relation between pain and sleep quality is two-way: sleep disorders can increase pain, which in turn may cause sleep disorders. Pain is a core symptom of AS, therefore, it is unsurprising that the sleep disorders and ankylosing spondylitis (AS) can co-exist. This cross-sectional study was designed to evaluate the impact of AS on sleep and nocturnal pain in adolescents with AS patients.

Patients and Methods: Patients were recruited from the rheumatology department and completed a battery of questionnaires from May 2010 to November 2010. Pittsburgh Sleep Quality Index (PSQI) and visual analogue scale (VAS) were used to assess sleep quality and nocturnal pain. Disease activity was assessed by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR). Data were analyzed by the SPSS 17.0 software.

Results: One hundred and fifty seven consecutive patients with AS (117 men, 40 women) were included in the study. The mean age of patients was 27.6 (SD ±4.9) years, and the mean disease duration was 6.1 (SD ±2.9) years. The mean PSQI and nocturnal pain score of patients was 6.1 (SD ±2.9) respectively. A total of 35.0% (55/157) of our AS participants had poor sleep. Quality of sleep was positively correlated with nocturnal pain (r=0.516, p≤0.001). In hierarchical multiple regression analysis, the quality of sleep variable contributed significantly to the variance in nocturnal pain score, adding an additional 18.2% to the overall R-square beyond that accounted by demographic and disease-related variables (R²=0.175).

Conclusion: Sleep quality has closely relationship and significant impact on nocturnal pain. These results highlight sleep disturbances could not be ignored in the management of AS.

P53
VALIDITY AND RELIABILITY OF THE IPAQ AND SQUASH TO ASSESS DAILY PHYSICAL ACTIVITY IN PATIENTS WITH ANKYLOSING SPONDYLITIS
Arends S.1,2, Hofman M.1,2, Kamsma Y.P.T.1, van der Veer E.1, Leijima M.K.1, Houtman P.M.1, Kallenberg C.G.M.1, Spoorenberg A.1,2
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Introduction: Due to participant convenience and minimal cost, physical activity questionnaires are considered to be the most applicable method to assess daily physical activity in population studies. The International Physical Activity Questionnaire (IPAQ) and the Short Questionnaire to Assess Health-enhancing physical activity in population studies (SQUASH) are widely used for this purpose. Our aim was to investigate the measurement properties of these questionnaires in patients with ankylosing spondylitis (AS).

Methods: The self-report questionnaires IPAQ (long form) and SQUASH were compared with daily physical activity assessed using the Actigraph accelerometer during 7 consecutive days (gold standard) in 63 patients. The IPAQ and SQUASH were administered on two different occasions one week apart in 52 patients. All patients fulfilled the modified New York criteria for AS or the ASAS criteria for axial spondyloarthritis. Validity was assessed by Spearman and Pearson correlations between accelerometer activity counts and IPAQ and SQUASH total scores. Test-retest reliability of the IPAQ and SQUASH was assessed by intraclass correlation coefficients (ICC) and Bland-Altman analysis.

Results: Mean age of the 115 AS patients was 45 years (SD±12), median duration of symptoms was 16 years (range 0-54), and 62% were male. IPAQ and SQUASH total score had good correlation significantly with accelerometer outcome: r=0.38 and r=0.35, respectively. ICC’s between first and second assessments of the IPAQ and SQUASH were 0.83 and 0.89, respectively. Bland-Altman analyses showed no systemic bias, in particular for the IPAQ the 95% limits of agreement were wide.

Conclusions: Both physical activity questionnaires showed moderate construct validity. The SQUASH showed good test-retest reliability, superior to the IPAQ. These results indicate that the SQUASH can be used to assess daily physical activity in AS population studies.
rent cardiovascular disease or systolic myocardial dysfunction, who were eligible to anti-TNF therapy, were prospectively enrolled. All patients received TNF blockers (infliximab, adalimumab and etanercept in their regular schedule) and they were evaluated for circulating NT-proBNP levels, clinical and laboratory parameters of disease activity including BASDAI, ASDAS, ESR and CRP, traditional cardiovascular risk factors including blood pressure, body mass index, waist circumference and dyslipidemia; conventional and tissue Doppler imaging echocardiography and treated with baseline (BL) and six months after (6M). Results: At BL, all patients had active AS, NT-proBNP levels had a median of 36 (20-72)pg/ml and 11% were high in spite of no systolic alteration. Multiple linear regression analysis revealed that this peptide, at BL, was independently correlated with ESR (p=0.001), age (p=0.01) and pulse pressure (p=0.01). After 6M, all disease parameters improved and NT-proBNP levels were significantly reduced [24 (16-47) pg/mL, p=0.037] compared to BL. Changes in NT-proBNP were positively correlated with ESR changes (r=0.41, p<0.006). Cardiovascular risk factors remained unchanged during follow-up.

Conclusions: Elevations of NT-proBNP should be interpreted with caution in active AS patients with no evidence of cardiovascular disease. The short-term reduction of NT-proBNP levels in these patients treated with anti-TNF therapy appears to reflect an improvement in inflammatory status.

P56
HIGH SENSITIVE CRP LEVELS CORRELATE WITH BASDAI IN AXIAL SPA

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Introduction: hs CRP and SR are objective markers of systemic inflammation, not influenced by psychological factors. Slightly elevated hsCRP has been shown to increase cardiovascular risk and risk of osteoporotic fracture. There has been a lack of correlation between standard CRP levels and clinical markers of disease activity such as BASDAI in axial SpA. As routine assays have limited sensitivity in detection low levels of CRP, we investigated the usefulness of a High sensitive CRP (hsCRP) assay in Axial SpA.

Materials and Methods: A total of 320 patients (185 women and 135 men) with inflammatory back pain were included in the study. They fulfilled ESSG-criteria for SpA. 70 patients or fulfilled New York criteria for Ankylosing Spondylitis. 44% were HLA B27 positive and 30 % had positive MRI for sacroiliitis. Median age 49 years and median disease duration 19 years. The mean level of BASDAI was 4.3±4.8 for men and women. The difference was significant with p-value 0.046. 40% of CRP was measured using Cobas IntegracR in the lowest detected level 0.71 mg/L. Nonparametric statistical analyses were performed.

Results: The median/mean levels of hsCRP was 5.7/2.3 range 0.0-133. There was no difference for hsCRP between male and female, or between radiographic and non-radiographic SpA. The correlation between SR and BASDAI was significant with Spearman’s rho 0.117, p-value 0.039. The correlation between CRP was significant with Spearman’s rho 0.118, p-value 0.036.

Conclusion: HsCRP correlates with BASDAI in axial SpA, and could be used in estimating disease activity possibly as a cardiovascular risk predictor.

P57
ASSESSMENT OF THE T1W MRI SHOULD BE INCLUDED IN THE DEFINITION OF A POSITIVE MRI OF THE SACROILIAC JOINTS IN SPONDYLOARTHRITIS

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Background: Inflammation on MRI of the sacroiliac joints (SIJ) in patients with SpA is a major criterion in the Assessment of SpondyloArthritis (ASAS) classification criteria for axial SpA, which are based on expert clinical opinion as gold standard. Studies using a data-driven approach to defining a positive SIJ MRI are scarce. We aimed to assess candidate definitions for a positive MRI using both clinical gold standard and confidence in the diagnosis of SpA according to global evaluation of the MRI scan on a 0-10 scale (0 = definitely not; 10 = definite). An MRI-based gold-standard criterion for SpA was pre-defined as the majority of readers recording a confidence of 8-10. We estimated the type and extent of involvement according to both clinical and MRI-based gold-standard criteria.

Methods: In this exploratory cross-sectional study, 189 unrelated anti-tumour necrosis factor naïve Dutch Caucasian AS patients were included and CRP SNPs rs2794521, rs3091244, rs1800947, and rs876538 were genotyped and haplotypes constructed. A multivariate linear and logistic regression model to investigate the relation between the SNPs and baseline CRP levels (mg/l), controlling for NSAID use, BMI, smoking, age, sex, and using the BASDAI to correct for disease activity.

Results: CRP levels were significantly positively correlated with the BASDAI (p<0.001). AS patients with genotype CA of the tri-allelic (C>T>A) SNP rs3091244 had a significantly higher odd ratios compared to either lesion alone without reducing specificity irrespective of which gold standard criterion was used.

Conclusions: This data driven study shows that assessment of the T1W sequence enhances diagnostic certainty when viewed simultaneously with the STIR and supports the case for revision of the ASAS definition of a positive MRI.

P58
C-REACTIVE PROTEIN (CRP) POLYMORPHISMS AND HAPLOTYPES INFLUENCE SERUM CRP LEVELS INDEPENDENT OF DISEASE ACTIVITY (BASDAI) IN ANKYLOSING Spondylitis

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Background: C-reactive protein (CRP) levels are used more frequently for determination of disease activity in patients with Ankylosing Spondylitis (AS), but these levels do not necessarily reflect disease activity in each patient. Aims: We investigated whether CRP levels were influenced by common single-nucleotide polymorphisms (SNPs) and haplotypes in the CRP gene in AS patients. Additionally, we studied the relation between CRP levels and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

Methods: In this exploratory cross-sectional study, 189 unrelated anti-tumour necrosis factor naïve Dutch Caucasian AS patients were included and CRP SNPs rs2794521, rs3091244, rs1800947, and rs876538 were genotyped and haplotypes constructed. We used a multivariate linear and logistic regression model to investigate the relation between the SNPs and baseline CRP levels (mg/l), controlling for NSAID use, BMI, smoking, age, sex, and using the BASDAI to correct for disease activity.

Results: CRP levels were significantly positively correlated with the BASDAI (p<0.001). AS patients with genotype CA of the tri-allelic (C>T>A) SNP rs3091244 were associated with significantly higher CRP levels when compared with genotype CC (CA: 18.6 mg/l vs. CC: 8.3 mg/l; p=0.05) in the multivariate regression model. Heterozygous carriers of haplotype 5 (tagged by allele A of rs3091244) had a significantly higher odd ratio compared to either lesion alone without reducing specificity irrespective of which gold standard criterion was used.

Conclusions: Certain CRP polymorphisms (SNP rs3091244 genotypes) and the haplotype tagged by allele A are associated with higher CRP levels in AS, independent of the BASDAI and other confounders. Therefore, carrying distinct genetic variants might explain the lack of elevated CRP levels despite high disease activity in
certain AS patients. This observation can be important to interpret disease activity scores that incorporate CRP levels, like the Ankylosing Spondylitis Disease Activity Score (ASDAS).

**PS9**

**EPITISATION BETWEEN TWO HLA ANTIGENS DEFINES A SUBSET OF INDIVIDUALS AT A VERY HIGH RISK FOR ANKYLOSING SPONDYLITIS**

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**Objectives:** Susceptibility to spondyloarthritis is largely genetically determined. To understand increasingly complex genetic associations, one approach is to study epitasis or genetic interactions. Several diseases associated HLA-antigens are known for SpA including HLA-B27. In this study, we investigated epitasis between common HLA class I risk antigens in ankylosing spondylitis (AS) the most typical form of SpA.

**Methods:** In 154 patients with AS and 5584 controls, HLA class I antigens were analyzed for association with AS. Biologic interaction was analyzed by investigating whether the effects of the risk factors combined depended from additivity.

**Results:** Apart from the association with HLA-B27, we found an association between HLA-B60 and AS (OR 1.8, 95%CI 1.2-2.8). This was confirmed in meta-analysis of published data (OR 2.2, CI 1.8 – 2.8). While 18.2% of AS patients had both HLA-B27 and HLA-B60, this combination was found in only 0.4% of controls. Using AS patients without HLA-B27 and HLA-B60 as reference, the relative risk (RR) for disease in HLA-B27+/HLA-B60+ patients was 1.2 (CI 0.3-4.1). For HLA-B27+/HLA-B60- the RR was 69 (CI 40-111) but increased to 342 (CI 147-708) in HLA-B27+/HLA-B60+ patients. For the interaction, the relative excess risk (REER) was 251, the attributable proportion (AP) was 0.8, and the synergy index (S) 4.7. The interaction was confirmed in an independent cohort.

**Conclusion:** There is a strong epitassic interaction between HLA-B60 and HLA-B27 in AS susceptibility. As a result, individuals with the HLA-B27+/HLA-B60+ genotype are at a very high risk of developing AS.

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**P60**

**KILLER IMMUNOGLOBULIN RECEPTORS 3DL1 AND 3DL2 BINDING TRACKS CLOSELY WITH SURFACE EXPRESSION OF MHC CLASS I FREE HEAVY CHAIN AND HLA B27 EXPRESSING ABNORMAL PEPTIDES BUT DOES NOT DISTINGUISH B27 SUBTYPES ASSOCIATED WITH ANKYLOSING SPONDYLITIS**

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**Introduction:** Ankylosing spondylitis (AS) is strongly associated with the HLA B27 subtypes B2704 and 2705 but not with B2706 and 2709. The correlation of KIR3DL1 and 3DL2 binding follows surface expression of FHC and MARB4 staining. MARB4 might be detecting a subgroup of HLA B27-peptide complexes identified by KIR or they be cross reacting with FHC dimers.

**Conclusion:** KIR3DL1 and KIR3DL2 binding follows surface expression of FHC and MARB4 staining. MARB4 might be detecting a subgroup of HLA B27-peptide complexes identified by KIR or they be cross reacting with FHC dimers.

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**P61**

**A GENOMEWIDE ASSOCIATION STUDY OF ANTERIOR UVEITIS**

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**Introduction:** Anterior uveitis (AU) is the most common extra-articular manifestation of ankylosing spondylitis (AS), occurring in up to 30-40% of AS cases. The aim of the current study was to investigate clinical associations of AS, and to identify genes associated with the risk of developing AU.

**Methods:** 972 AS cases with AU (AS+AU+) and 1404 AS cases without AU (AS+AU-) were available for study. All cases were of white European descent. A genomewide association study was performed using SNP data from the TASC and TASC-WTCCC2 AS studies. 291,537 SNPs were available in the merged data set. Case-control analysis comparing the AS+AU+ and AS+AU- cohorts was performed using Eigenstrat to control for population stratification effects.

**Results:** Male and female AS cases were equally likely to develop AU. As expected, AU complicating AS was strongly associated with AS disease duration (beta=0.027, p<10^-6). No association was seen with age, independent of AS disease duration. Considering AS+AU+ cases in comparison with AS+AU- cases, no SNP achieved genomewide significance. Three loci showed suggestive association with AU. At chromosome 6q26, two SNPs in the PARK2 gene achieved p<10^-6 (rs8249576, p=7.6x10^-6; rs13205287, p=2.0x10^-6). Five SNPs (rs379796, rs419519, rs445890, rs452186, rs45218) in an intergenic region on chromosome 4q33 achieved p<9.5x10^-6. Association with HLA-B27 (antigen carriage, odds ratio 3.1, p=5.6x10^-4). There was a marginal association of B27-homozgyosity in this analysis (odds ratio 2.1, p=0.06). No known AS locus was differentially associated in AS+AU+ cases in comparison with AS+AU- cases.

**Conclusion:** This analysis found that with the exception of HLA-B27, no differences were identified between AS+AU+ and AS+AU- cases. The study was adequately powered to identify moderately large genetic effects, but not small-moderate genetic effects for which larger studies will be required. Further, as all patients studied have AS, whether genetic associations of AS+AU cases are different to those of AS+AU remains unclear.

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**P62**

**INVESTIGATING THE GENETIC ASSOCIATION BETWEEN ERAPI AND SPONDYLOARTHRITIS**

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**Aim:** A robust association was recently identified between polymorphisms in the ERAP1 gene encoding the peptidase responsible for hitoscompatibility complex gene ERAPI and ankylosing spondylitis (AS) in several populations. The aim of the current study was to determine the level of association of ERAPI polymorphisms with spondyloarthritis (SpA) in French/Belgian populations with a particular attention to genotype-phenotype correlations.

**Methods:** We studied 734 independent SpA cases and 632 controls from 2 European cohorts. Five single nucleotide polymorphisms (SNPs), rs27044, rs17482078, rs10050860, rs30187 and rs2287987 were genotyped and case-control association
analyses were carried using PLINK. Linkage disequilibrium and haplotypes were estimated with Haploviz. Analysis was first carried in SpA as a whole group, and then separately in AS and non-radiographic SpA (non-AS) patients.

Results: Consistent with previous studies conducted in AS, rs30187 was the most significantly associated SNP with SpA (p=0.008 in the French and p=6.46×10^{-10} in the Belgian cohorts). In the combined cohort, this SNP was associated with both AS and non-AS (Pcombined=9.08×10^{-8}), including AS and non-AS (Pcombined=1.66×10^{-10} and Pcombined=6.04×10^{-4}, respectively), whereas the -TTC haplotype was associated with reduced risk of SpA, including AS and non-AS (Pcombined=2.36×10^{-6}/Pcombined=5.69×10^{-4} and Pcombined=2.13×10^{-4}, respectively).

Conclusion: This is the first study to show an association between several polymorphisms located in ERAP1 and SpA as a whole. Our findings demonstrate consistent association of the same SNPs and haplotypes with both AS and non-AS subtypes of SpA.

P63

THE NON-SYNONYMOUS POLYMORPHISM IL23R ARG381GLN IS ASSOCIATED WITH ANKYLOSIS IN SPONDYLOARTHITIS

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Objective: Spondyloarthritis (SpA) is a group of articular disorders sharing genetic background. Single-nucleotide polymorphisms (SNP) of the interleukin 23 receptor (IL23R) gene have been reproducibly reported as associated with ankylosing spondylitis (AS) a subset of SpA, defined by advanced radiographic sacroiliitis. Here, we examined the association between several SNPs in the IL23R gene and SpA as a whole. A particular attention was devoted to genotype-phenotype correlations.

Methods: Eight single-nucleotide polymorphisms (SNPs) located in the IL23R gene were genotyped in a collection of 414 independent French SpA patients and in 264 healthy controls. In addition, the most significantly associated polymorphism (rs11209026 Arg381Gln) was genotyped in 156 multiplex families of SpA and in 136 independent trios. Association analyses were carried using UNPHASED, in AS as a whole group, and then separately in AS and non-radiographic SpA (non-AS) patients.

Results: Strong association with AS was observed in the 3 datasets (case/control, familial and trios) with the non-synonymous polymorphism rs11209026 Arg381Gln (p=8.26×10^{-4}/p=4.59×10^{-4} and p=9.02, respectively). In contrast, such association was not detected with the non-AS group (p=0.878/p=0.65 and p=1). Furthermore, association with this polymorphism was significantly different between the AS and non-AS patients in both studies (p=2.5×10^{-4}).

Conclusion: Our results confirm that IL23R polymorphisms are associated with SpA, either in sporadic or in familial cases. However, phenotypic analysis revealed that association with Arg381Gln polymorphism is restricted to the AS subtype, suggesting that IL23R could influence the phenotypic expression of SpA by promoting ankylosis.

P65

A SPARCCE-SCORE CUT-OFF ≥3 AS BEST MATCH FOR THE ASAS DEFINITION OF A POSITIVE MRI OF THE SACROILIAC JONTS

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Introduction/Aim: The definition of a ‘positive’ or ‘negative’ MRI of the sacroiliac joints (MRI-SIJ) according to ASAS is recommended for use in daily practice. However, in several clinical trials the SPondyloArthritis Research Consortium of Canada (SPARC) score is used. Which SPARC-score cut-off value best matches the ASAS definition for a positive MRI-SIJ?

Patients and Methods: All MRI-SIs of two time points (baseline and 3 months) of patients included in the SPondyloArthritis Caught Early (SPACE)-cohort in the Leiden University Medical Center (LUMC) were scored independently by 3 readers. The readers, blinded to the time sequence, scored the MRI-SIs according to the ASAS definition (ASAS-pos) and the SPARC-score. An MRI-SIJ was marked ASAS-pos if ≥2 readers scored positive. In this analysis, mean SPARC-score of the readers that also scored ASAS-pos for that particular case were used. Cross-tabs were used to analyse agreement between several SPARC-score cut-off values (a1, a2, a3 and a4) and ASAS-pos, which are used as external standard in this comparison.

Results: All available MRI-SIs were used (n=238 in total; n=148 baseline MRI-SIs; n=90 follow-up MRI-SIs). The results of the different tested SPARC cut-off values are presented in the table. A SPARC cut-off value a2 resulted in 11 (4.6%) false-positive classifications and no false-negative classifications, compared to ASAS-pos, while a cut-off of ≥3 resulted in 9 (3.8%) false-negative and 1 (0.4%) false-positive classifications. A SPARC cut-off value a3 resulted in 1 (0.4%) false-positive classification and 4 (1.7%) false-negative classifications. We found very similar results if baseline MRI-SIs and follow-up MRI-SIs were analysed separately.

Conclusions: SPARC cut-off values of a2, a3 or a4 have all high percentages of correctly classified patients (95.4%, 97.9% and 95.8%, respectively). A SPARC cut-off value ≥3 shows most balanced misclassification and the highest agreement with the ASAS definition for a positive MRI-SIJ.

Poster Presentations

Eighth International Congress on Spondyloarthritis

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LOCALISATION OF BONE MARROW EDEMA IN SACROILIAC JOINTS IN SpondyloArthritis Patients: DOES THE SITE OF LESIONS CHANGE OVER A 3-MONTH PERIOD?

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Introduction/Aim: A positive MRI at baseline is a strong predictor for a positive follow-up MRI. But many questions about the volatility of the lesions over short follow-up periods remain unsolved. The objective is to describe if and how locations of active inflammatory lesions change and if lesions can disappear, occur or move location over time without changing treatment.

Patients and Methods: 90 patients with chronic back pain (≥3 months, ≥2 years, onset ≥45 years) included in the SPondylitis Arthritis Caught Early-Cohort underwent STIR and T1 MRI of the SI-joints at baseline and after 3-month follow-up.

Results: Table 1 shows the lesions and their location at baseline and at follow-up. The quadrant in which the lesion was present did not change over time in 6 patients. Lesions disappeared from quadrants in 9 patients (lesion disappeared in only 1 quadrant in 7 patients and in 3 quadrants in 2 patients) and occurred in 7 patients (MRI changed from negative to positive in 5 and remained positive in 2 patients). In 2 patients, the lesions moved between quadrants (disappear from one and occurred in another). In 20/24 patients medication did not change during follow-up (18 patients used NSAID, 2 did not use medication) and 4 patients changed medication (2 patients switched NSAID type and 2 started NSAID treatment). Out of the patients that changed from a negative to positive MRI (n=5) or visa versa (n=4), only 1 patient also changed medication, by switching to another NSAID. Conclusions: BME lesions on MRI occur or disappear at SIJ-level in 9% of the patients after 3 months. In 50% of patients with a positive MRI at baseline, lesions did not change location at SIJ level while; at quadrant level, less than 30% of the patients showed stability in the location of lesions. So, there is quite some volatility of lesions over a short follow-up period of 3 months only.

No. of patients 3-month follow-up

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</tbody>
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P68

NEW SCORING SYSTEM FOR RADIOGRAPHIC SACROILIITIS: A WAY TO FOLLOW DIFFERENT STRUCTURAL CHANGES

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Aim: The objective of the study was to correlate the progression of radiographic sacroiliitis in the standard score with the dynamics of different structural changes in the sacroiliac joints reflected in a new scoring system in patients with axial spondyloarthritis (SpA).

Material and Methods: Standard plain radiographs of sacroiliac joints of 103 patients (206 joints) with definite axial SpA from the German Spondyloarthritis Inception Cohort (GESPIC) performed at baseline and after 4 years of follow up were scored according to the modified New York criteria (grade 0 to grade IV) and according to the proposed scoring system. Proposed system implements separate scores for 1) subchondral sclerosis, 2) erosions, 3) joint space in each sacroiliac joint.

Results: Radiographic progression by at least one grade (according to the modified New York criteria) over 4 years occurred in 28.2% of the joints, the highest progression rate (53.3%) was observed in joints with grade 0 at baseline, grade I worsened in 29.8%, grade II I – in 37.5% and grade III – in 12.8% of the joints. Both, destructive (erosions) and reparative (subchondral sclerosis), processes start simultaneously and are both responsible for the progression of sacroiliitis at the early disease stage (sacroiliitis grade 0 and I at baseline). Progression of sacroiliitis with initial grade II was mostly related to the dynamic of erosions (worsening in 50% of the joints, but also improvement in another 22.3% of the joints) and joint space changes (in almost 90% of the joints), while subchondral sclerosis remained unchanged in the majority of the cases. At the same time, progression from grade III to grade IV was attributable not only to ankylosis formation, but also to improvement of sclerosis and, to a lesser extent, erosion score indicating finalization of the bone repair.

Conclusion: Progression of radiographic sacroiliitis is related to different structural processes at different disease stages that should be taken into account while assessing disease progression in axial SpA, especially at the early stage.

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ASSESSING ACTIVE INFLAMMATION IN SACROILIAC JOINTS IN SpondyloArthritis Patients: NO ADDED VALUE OF GADOLINIUM COMPARED TO STIR SEQUENCE

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Introduction/Aim: T1 weighted and STIR images are generally used as a diagnostic tool to detect abnormalities of the sacroiliac joint (SIJ). The ASAS definition of a positive MRI for SpA is based on bone marrow edema (BME). Imaging after intravenous administration of gadolinium (Gd) may improve detection of active lesions compared to STIR sequence. Therefore we investigate the additional value of T1 fat sat after Gd (T1/Gd), compared to T1 and STIR sequence in the detection of BME, synovitis and/or capsulitis/enthesitis of the SIJ and assess its influence on final MRI diagnosis based on the ASAS definition.

Patients and Methods: All patients included in the SpondyloArthritis Caught Early-project received MRI of the SIJ (MRI-SIJ). Acquired sequences were coronal oblique T1, STIR and T1/Gd at baseline and after 3 months follow-up. BME, synovitis and capsulitis/enthesitis were scored on STIR as well as T1/Gd and compared in conjunction with unenhanced T1 images. A positive MRI was defined as presence of BME on STIR according to the ASAS definition. Scoring was done by three blinded trained readers. MRI was considered positive if 2 out 3 readers stated positive.

Results: No additional BME was found on the T1/Gd. At baseline, 7 patients (5.5%) showed synovitis and/or capsulitis/enthesitis, in addition to present BME. Patients with capsulitis also showed synovitis. One patient (0.8%) showed synovitis as an isolated finding and did not fulfill the ASAS, ESSG, Amor or modified New York classification criteria. All patients with a positive MRI, capsulitis or synovitis at follow-up showed this finding also at baseline (table 1).

Conclusions: STIR sequence by itself is sufficient to detect active sacrolilitis according to the ASAS definition. Synovitis, capsulitis/enthesitis observed with gadolinium, is seen in the presence of BME, except in one patient without clinical signs of SpA. In line with the recommendations by ASAS, our data show that Gd is not needed in the MRI assessment of patients with SpA.

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NO EVIDENCE FOR A ROLE OF THE HYPOTHESIZED SE-QUENCE INFLAMMATION – FATTY DEGENERATION – NEW BONE FORMATION IN PATIENTS WITH ANKYLosing SPONDY-LITIS TREATED WITH ANTI-TNF AGENTS OVER 5 YEARS

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Introduction/Aim: The effect of anti-TNF on new bone formation in ankylosing spondylitis (AS) is still unclear. An often discussed hypothesis (‘TNF brake’) suggests that synovymphocytes develop in vertebral edges (VE) after resolution of inflammation (INF) and development of fatty degeneration (FD) due to anti-TNF agents. We compared the influence of INF and/or FD on the development of synovymphocytes in AS after 2 and 5y of anti-TNF therapy.

Methods: MRIs and x-rays from 73 patients from EASIC were read in concealed time order. Most patients were treated with infliximab, some with other TNF blockers. Presence or absence of INF, FD and synovymphocytes was documented on the level of VE's. Data were analysed using Fisher’s exact test.

Poster Presentations
Results: Overall, 804 VEs without syndesmophytes or ankylosis at baseline were analysed. 3.9% syndesmophytes developed at 5y from VEs showing only FD at baseline, whereas no syndesmophytes developed in VEs with only INF at baseline (p<0.05). When FD and INF were both present at baseline, 4.9% syndesmophytes developed by 5y. In detail, out of VEs with INF but no FD at baseline, 27.6% turned into FD at 2y, but none of these developed a syndesmophyte at 5y. The vast majority of those 61 VEs which had both, INF and FD, at baseline continued to have FD at 2y (97%), 3 of which gave developed a syndesmophyte at 5y (4.9%). Out of VEs without INF or FD at baseline (n=438), 21.5% VEs and another 3% developed FD at 2y and at 5y, respectively.

Conclusions: The hypothesized sequence inflammation - fatty degeneration - new bone formation was not observed in patients with AS treated with anti-TNF agents over 5 years. Although there was a high proportion of VEs with INF at BL that developed FD at 2y, that was not followed by new bone formation at 5y.

Results: Mean symptom duration of the study population (N=185) was 10 years. At baseline, 48% of patients were reported by the local investigator to have past or present MRI evidence of sacroiliitis according to ASAS axial SpA criteria. Of those with available data, 40% had baseline SII score ≥2 and 52% had baseline spine score ≥2. Of patients with baseline SPARCC SII score ≤2, 49% had a baseline SPARCC spine score ≥2. Baseline disease characteristics of patients with baseline spine score ≥2 vs ≤2 were generally comparable except for mean age (36 vs 40 years) and SPARCC SIJ scores (3.2 vs 6.5); likewise for patients with baseline SII score ≥2 vs ≤2, except for gender (46% vs 44% female).

Conclusions: Spinal inflammation on MRI was observed in half of nr-axSpA patients without SII inflammation on MRI. Imaging both sites might be valuable when evaluating for nr-axSpA. As patients had long-standing disease, these data need to be confirmed in patients with shorter disease duration.

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IS THERE A ROLE FOR HEDGEHOG PROTEINS IN THE DEVELOPMENT OF SYNDESMOHYTES IN PATIENTS WITH ANKYLOSING SPONDYLOARTHRITIS?

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Introduction/Aim: The Hedgehog (Hh) molecules consist of three different protein groups (Sonnc Hh (SHh), Indian Hh (Ihh) and Desert Hh (Dhh)) and represent an important pathway for the development of chondrocytes and enchondral ossification. Hh signaling can influence a pathological chondrocyte hypertrophy in the articular cartilage in osteoarthritis. No data about its effect on spinal new bone formation in AS have been generated to date. We examined the role of Hh proteins as predictors of syndesmohyte (synd) formation in AS patients.

Methods: Patients from EASAC with complete data sets of sera and conventional radiographs of the cervical and lumbar spine at baseline (BL), 2y and 5y were analysed. Serum levels of Hh proteins were measured by ELISA. Velocities for radiographic progression were defined for slow, moderate and fast progressors, as recently proposed. Analysis of variance based on rank transformed data (van der Waerden scores) were used to compare patient groups.

Results: Serum levels of Dhh showed almost a dose response pattern related to the different groups of radiographic progression (P<0.043): the mean serum level for slow progressors was 20.1 ng/mL (95% CI 1.3-39.0), for moderate progressors 31.0 ng/mL (95% CI 2.2-59.8) and for fast progressors 43.9 ng/mL (95% CI 17.4-70.2). Furthermore, there was also a trend for higher baseline levels of SHh (P=0.076), but no signal was seen for Ihh. Hh levels did not correlate with radiographic damage at BL in this study.

Conclusions: This is the first study to investigate serum levels of Hedgehog proteins in patients with active AS with respect to syndesmohyte development. Although different serum levels of Desert Hedgehog seemed to differentiate well between fast and slow radiographic progression, there was no apparent correlation of serum levels of Hh proteins and radiographic damage or progression. Furthermore, there was a trend for a positive signal related to SHh but not Ihh.

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CONCURRENT SACROILIAC JOINT AND SPINAL INFLAMMATION ON MRI IN PATIENTS WITH NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS

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Introduction/Aim: The imaging arm of the ASAS axial spondyloarthritis (SpA) criteria requires sacroiliitis on MRI or radiographs. In non-radiographic axial SpA (nr-axSpA) patients there may be spinal inflammation without sacroiliac joint (SIJ) inflammation.

Methods: ABILITY-1 is an ongoing randomized, controlled trial of adalimumab vs placebo in patients with AS fulfilled ASAS axial SpA criteria but not modified New York criteria for AS) who had an inadequate response, intolerance, or contraindication to NSAIDs. MRI of the SIJ and spine were performed at baseline and week 12, and were centrally read using the SPARC method. The proportion of patients with SPARCC score ≥2 at baseline for either the SIJ or spine was evaluated.

Results: Overall, 804 VEs without syndesmophytes or ankylosis at baseline were analysed. 3.9% syndesmophytes developed at 5y from VEs showing only FD at baseline, whereas no syndesmophytes developed in VEs with only INF at baseline (p<0.05). When FD and INF were both present at baseline, 4.9% syndesmophytes developed by 5y. In detail, out of VEs with INF but no FD at baseline, 27.6% turned into FD at 2y, but none of these developed a syndesmophyte at 5y. The vast majority of those 61 VEs which had both, INF and FD, at baseline continued to have FD at 2y (97%), 3 of which gave developed a syndesmophyte at 5y (4.9%). Out of VEs without INF or FD at baseline (n=438), 21.5% VEs and another 3% developed FD at 2y and at 5y, respectively.

Conclusions: The hypothesized sequence inflammation - fatty degeneration - new bone formation was not observed in patients with AS treated with anti-TNF agents over 5 years. Although there was a high proportion of VEs with INF at BL that developed FD at 2y, that was not followed by new bone formation at 5y.

Results: Mean symptom duration of the study population (N=185) was 10 years. At baseline, 48% of patients were reported by the local investigator to have past or present MRI evidence of sacroiliitis according to ASAS axial SpA criteria. Of those with available data, 40% had baseline SII score ≥2 and 52% had baseline spine score ≥2. Of patients with baseline SPARCC SII score ≤2, 49% had a baseline SPARCC spine score ≥2. Baseline disease characteristics of patients with baseline spine score ≥2 vs ≤2 were generally comparable except for mean age (36 vs 40 years) and SPARCC SIJ scores (3.2 vs 6.5); likewise for patients with baseline SII score ≥2 vs ≤2, except for gender (46% vs 44% female).

Conclusions: Spinal inflammation on MRI was observed in half of nr-axSpA patients without SII inflammation on MRI. Imaging both sites might be valuable when evaluating for nr-axSpA. As patients had long-standing disease, these data need to be confirmed in patients with shorter disease duration.
IS ENTHESIS THE PRIMARY IMMUNOPATHOLOGICAL LESION IN HLA-B27-ASSOCIATED EXPERIMENTAL AND HUMAN SPONDYLOARTHRITIS?

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Introduction/Aim: Anti-TNF therapy is clinically efficacious in patients with ankylosing spondylitis (AS) but there is no evidence that it inhibits new bone formation. Biomarkers of increased bone turnover like bone alkaline phosphatase (BAP) and sclerostin (SCL) play a role in new bone formation in AS. We studied the influence of serum levels of SCL and BAP and prevalent syndromes on the syndromes in development in AS.

Methods: Patients from EASIC with complete data sets of sera and conventional radiographs of the cervical and lumbar spine at baseline (BL), 2y and 5y were analysed. BAP and sclerostin were measured by ELISA. Velocities for radiographic progression were defined for slow, moderate and fast progressors, as recently proposed. Analysis of variance based on rank transformed data (van der Waerden transformed) was performed.

Results: Sclerostin levels at BL were significantly lower in patients with syndromes than at BL (0.8±0.3 pg/ml), than in those without (1.1±0.5 pg/ml), p<0.009. There was no significant difference in BL-sclerostin levels in the 3 groups with different velocity of radiographic progression after 2y and 5y. There was no correlation of BAP at BL and radiographic progression after 2y and 5y.

Conclusion: In contrast to an earlier study we found no predictive value of sclerostin levels for new bone formation in AS in this trial with anti-TNF treated patients. Whether this is due to the anti-TNF treatment remains unclear at present. However, sclerostin levels did correlate with BL radiographic damage, but they did not differentiate between different types of progression.

EVOLUTION OF RADIOGRAPHIC DAMAGE IN ANKYLOSING SPONDYLITIS OVER 12 YEARS OF FOLLOW-UP

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Background: Radiographic damage is one of the core outcomes recommended by the ASAS for follow-up of patients with AS. So far, the evolution of radiographic damage over a long period of follow-up has not been described.

Objectives: To describe the evolution of radiographic progression in an observational cohort.

Methods: The modified Stoke AS Spine Score (mSASSS) was calculated using 2-yearly spinal radiographs of patients in OASIS followed for 12 years. Two readers independently scored the x-rays and averaged scores per vertebral corner (VC) were used. Status and progression scores (2-year and 12-year-progression) were computed, for all patients with at least one 2-year interval available (n=186) and for those with an mSASSS at 12-years (n=68). New syndesmophytes at VCs at risk (i.e. without a previous syndesmophyte or bridge) were computed, both at a radiograph and at a patient level.

Results: 809 radiographs in which the mSASSS could be scored were included in this analysis. The mean (SD) mSASSS was 15.8 (18.3) (17.4 (18.3) in patients with mSASSS available at 12-years). The mean (SD) 2-year interval progression score (in 520 two-year intervals) was 2.0 (3.5) (2.2 (3.5) for subset of 12-year-completers). Over the 12 years, the mean (SD) progression was 11.7 (11.5). A new syndesmophyte was assessed in 55-63% of the patients with at least one VC at risk and at least one 2-year mSASSS interval available. In 24% of the patients (39% of the 2-year intervals) there was no progression in mSASSS. A progression ≥1 mSASSS unit was observed in 72% of the patients (54% of the 2-year intervals) and a progression ≥5 mSASSS units in 22% of the patients (12% of the intervals).

Conclusion: Over a 12-year period of follow-up, radiographic progression in AS is variable. Three quarters of the patients have some progression and about 60% has at least one new syndesmophyte.
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RADIOGRAPHIC SCORE FOR AS: MSASSS VS RASSS

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Background: Radiographic damage is assessed on lateral cervical and lumbar spinal X-rays using the modified Stoke AS Spine Score (mSASSS), which misses the lower thoracic spine. The recently proposed Radiographic AS Spine Score (RASSS) includes the lower thoracic vertebrae, but its additional value over mSASSS is undetermined.

Objectives: To compare the mSASSS and RASSS with regard to efficiency and added value.

Methods: Both mSASSS and RASSS were calculated using 2-year interval spinal radiographs of patients in OASIS followed for 12 years. Status and 2-year progression scores were compared. The potentially added value of the 4 thoracic sites in the RASSS was determined by comparing the actually observed relative segmental contribution with the expected contribution if the progression pattern was balanced.

Results: 809 radiographs in which the mSASSS could be scored were included in this analysis. The RASSS could be calculated in 78% of these. In 58% of those, the RASSS was calculated based on 1 or 2 present scores, and the remaining 2 or 3 were imputed because of missing. 520 two-year mSASSS interval progression scores were available, and in 63% of them a 2-year RASSS score could be determined. Of all the radiographs in which both scores could be determined (n = 629), the mean SD status score was 15.5 (17.9) units for the mSASSS and 18.0 (20.9) units for the RASSS. The mean (SD) 2-year interval progression scores (in 330 two-year intervals) were 2.0 (3.6) for the mSASSS and 2.4 (4.4) for the RASSS. Exclusive progression of the thoracic segment occurred in only 5% of the cases. There were no significant differences between the observed (14%) and expected (16%) contribution to progression of the thoracic segment (p=0.692).

Conclusion: The determination of a RASSS is frequently impossible or strongly influenced by imputation. The contribution of thoracic VCs in the RASSS-method is negligible, and does not justify the additional scoring efforts.

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SUPERIORITY OF OPTICAL COHERENCE TOMOGRAPHY OVER ULTRASOUND FOR THE ASSESSMENT OF NAIL DISEASE IN PSORIASIS AND PSORIATIC ARTHRITIS

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Introduction: Clinical assessment is still the current gold standard for evaluation of psoriatic nail disease. This report compares Optical Coherence Tomography (OCT) and ultrasound (US) in the assessment of nail disease in psoriasis (Pso) and psoriatic arthritis (PsA).

Methods: A total of 300 finger nails of 18 patients (5 Pso, 13 PsA) and 12 healthy controls (HC) were scanned using OCT by an investigator blinded to the clinical details. Signal changes within the nail and contour abnormalities were documented using both modalities. Clinical onychopathy was independently scored by an assessor blinded to the OCT findings using the modified NAPSI scoring system.

Results: All patients had at least one clinically abnormal nail and 122 of 180 (67.8%) nails in this group were abnormal on physical examination. Fourteen patients (77.8%) had abnormalities seen by US and 15 (83.3%) were abnormal on OCT. None of all the HC had any clinical nail abnormalities. Having a positive OCT had a sensitivity (77.8%) and specificity of 44.4% and 95.8% respectively with a positive likelihood ratio of 2.07 (1.03-4.14) and negative likelihood ratio of 0.26 (0.06-1.03). OCT demonstrated 76.3% absolute agreement when compared to clinical assessment and 65% with US. Within psoriatic patients, OCT detected abnormalities in 17 (9.4%) clinically normal nails and in 41 nails (22.8%) where US assessment was normal.

Conclusion: These preliminary findings show that OCT has great potential for the systematic characterisation of nail changes in psoriasis. The role of OCT in the diagnosis, prognosis and monitoring of therapies in nail disease merits further evaluation.

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MRI ASSESSMENT OF SPINAL INVOLVEMENT IN PSA: EXTENT OF DISEASE RELATES TO HLA-B27

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Objective: To report the MRI prevalence of bone marrow oedema (BMO) lesions in symptomatic back pain in patients with Psoriatic Arthritis (PsA) in comparison with axial Spondyloarthritis (axSpA) and Ankylosing Spondylitis (AS).

Methods: Cross-sectional audit of MRI scans of the lumbar spine (LS) and SIJs. MRI scans were scored independently by two expert readers, blinded to the clinical characteristics of the patients using the semiquantitative Leeds MRI Scoring System (1). Concordant data from the two readers were used to report on definite lesions.

Results: MRI scans from 76 patients were available for analysis. Subjects were categorized into 3 groups: PsA, axSpA (non-radiographic patients that fulfilled the ASAS criteria for axial SpA) and AS (if patients fulfilled the mNYC). HLA-B27 positivity was similar in PsA (33.30%) and axSpA (41.67%) and higher in AS (50%). Total MRI scores (LS+SIJ) were higher in AS patients compared to PsA (p=0.025) and axSpA (p=0.007). Comparable amount of disease extent was shown by similar total number of BMO lesions both at the SIJ and LS in Psa, axSpA and AS patients but the number of severe lesions at the LS (grade ≥2) was higher in AS (p=0.01) and in PsA (p=0.03) than axSpA. When the groups were sub-analysed according to HLA-B27 status, a relationship was seen between the severity and extent of disease and HLA-B27 in the PsA group which was comparable to the AS group. HLA-B27 negative PsA patients had lower MRI scores than HLA-B27 positive PsA (p=0.03) and AS patients (p=0.006) whereas HLA-B27 positive PsA patients had similar scores to AS.

Conclusions: HLA-B27 related active PsA spondylitis shows a similar degree of MRI bone oedema as AS with a lesser degree of bone oedema in HLA-B27 negative PsA. These results suggest that the HLA-B27 subgroup of PsA share common aetiopathogenic mechanisms of disease with AS.

Reference:
**P80**

**COMPARISON OF CONVENTIONAL X-RAY WITH CT USING SA pissS FOR ANKYLOSING SPONDYLITIS PATIENTS**

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**Objective:** To compare conventional radiography and Computed tomography for evaluation of radiographic progression in ankylosing spondilitis

**Subjects and Methods:** All patient fulfilled the modified New York diagnostic criteria for AS. Assessment of radiographic progression in conventional x-ray and computed tomography was performed with Stobe Ankylosing Spondylitis Spinal Score. All images were read twice and blindly by two readers.

**Results:** Total 339 patients with AS were examined. Disease duration is less than 10 years and the mean age is 30.5±5.7 years. The proportion of male to female is 3:1 and 90.1% was HLA-B27 positive. Total SASS is 15.9±11.6 in X-ray and 19.7±8.3 in CT. In sclerosis, syndesmophyte and bridging CT detected more than X-ray, but did not in erosion and squaring, significantly. There were significant differences in SASS of conventional radiography versus those of CT in all L-spine level. Especially bone bridge and syndesmophyte was significantly detected when 3 dimensional reconstruction.

**Conclusion:** Conventional x-ray overestimates Erosion and squaring and under-estimates sclerosis, syndesmophyte and bridging. Our study suggests that the CT is more appropriate method than X-ray for assessing radiographic change in AS.

**Table. The results of SASS in subjects.**

<table>
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<th></th>
<th>X-ray (M,SD)</th>
<th>CT (M,SD)</th>
<th>3D(M,SD)</th>
<th>p-value</th>
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<tr>
<td>Erosion</td>
<td>246±8.7</td>
<td>211±9.3</td>
<td>105±6.6</td>
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</tr>
<tr>
<td>Sclerosis</td>
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<td>1860±11.5</td>
<td>1881±13.7</td>
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<tr>
<td>Squaring</td>
<td>10±19.6</td>
<td>717±9.6</td>
<td>561±4.5</td>
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<td>Syndesmophyte</td>
<td>159±4.5</td>
<td>316±10.3</td>
<td>464±10.9</td>
<td>&lt;0.05</td>
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<tr>
<td>Bridging</td>
<td>103±2.6</td>
<td>202±6.7</td>
<td>176±8.5</td>
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<tr>
<td>SASS</td>
<td>15.9±11.6</td>
<td>19.7±8.3</td>
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<td>&lt;0.05</td>
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</table>

**P81**

**SPINAL AND SACROILIAC INFLAMMATION AS DETECTED BY MAGNETIC RESONANCE IMAGING IN PATIENTS WITH ANKYLOSING Spondylitis, BEFORE AND AFTER 12 AND 52 WEEKS THERAPY WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS**

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**Objective:** To assess the inflammatory lesions of the spine and the sacroiliac joints (SII) as detected by magnetic resonance imaging (MRI) in patients (pts) with ankylosing spondylitis (AS) during 12 and 52 weeks treatment NSAIDs for the first time on daily basis.

**Methods:** 35 consecutive patients (pts) meeting the modified NY criteria AS were studied. MRI (T2 STIR and T1 MRI sequence, General Electrics, 0.35 T) scans were reviewed extensively using radiography as a reference. The second reading exercise was conducted as follows by the same expert readers on 25 AS patients at baseline (TP0), after 12 (TP1) and 52 (TP2) treatment NSAID’s weeks. For assessing active spinal lesions we used the scoring system modified ASspiMRI-a, and for SII - Leeds scoring system. The primary outcome measure were patient’s assessment of spine pain (NRS) and 50% reduction ASspiMRI-a and Lees scores. MR images were evaluated independently by 2 readers and one of them was blinded to the treatment allocation and time sequence of the images.

**Results:** Median age pts 33.2(23-60) yrs, 80% male, median disease duration 8.8 (1-20) yrs; 34 (97.1%) pts were HLA-B27 positive. Lumbar spine MRI were performed in 19 pts, thoracic spine - in 12, cervical -2, whole spine-2; SH - 32 pts, ASAS-NSAID Index 12 weeks satisfied 100, during 12-52 weeks – 62.5-100 (in accordance with clinical parameters). By 12 week patient’s assessment of spine pain reduced significantly from 4.8 (0-9) at TP0 to 2.6 (0-7.7) at TP1 (p<0.001). 42% pts achieved 50% reduction ASspiMRI-a; 10 (28.5%) pts – 50% reduction Lees score. Spinal inflammation decreased from 2.92 (0-11) at TP0 to 2.23 (0-9) at TP1 (p=0.051); Lees score reduced from 3.34 (0-10) to 2.21 (0-9) at TP1 (p=0.025). By 12 week 13% (37%) pts had ASDAS ≥4.0, respecting 24 (68.5%) pts at baseline (p=0.009), and were switched to TNF blockers. These pts at baseline had significantly longer AS duration (p=0.009), higher ASDAS (p=0.066), ASDAS (p=0.019) and pain in spine (p=0.008), but were fewer with pts with active saccroiliitis (p=0.028) and Lees score (p=0.0072).

By 52 week patient’s (n=22) assessment of spine pain reduced significantly from 4.5 (0-8) at TP0 to 2.7 (0-7) at TP2 (p=0.00144). 10 (45%) pts achieved 50% reduction ASspiMRI-a; 10 (45%) pts – 50% reduction Lees score. Spinal inflammation regressed from 2.44 (0-7) at TP0 to 1.5 (0-6) at TP2 (p=0.039); Lees score regressed from 3.43 (0-10) to TP0 to 1.9 (0-11) at TP2 (p=0.0095). Active lesions disappeared in 20% pts in spine (p=0.13) and in 22% in SII (p=0.08). By 52 week 22% pts had BASDAI ≤4.0 and were switched to TNF blockers.

**Conclusion:** NSAIDs decreased the level of pain in the most painful segment of spine and was effective enough for reducing imaging evidence of disease activity in patients with MRI determined inflammatory lesions.

**P82**

**MRI OF THE SPINE FOR DETECTION OF NEW BONE FORMATION IN ANKYLOSING SPONDYLITIS: DOES IT OFFER ANY ADVANTAGES OVER RADIOGRAPHY?**

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**Introduction:** Radiographic assessment of new bone formation in the spine is the current gold standard for detection of disease progression in ankylosing spondylitis (AS). However, sensitivity to change is limited and radiography cannot assess the thoracic spine. It is unclear whether MRI might offer any advantages over radio- graphy. We aimed to compare reliability of MRI with radiography, and to determine whether availability of radiographs enhances the reliability of detection on MRI.

**Methods:** We generated consensus definitions for bone spurs and ankylosis on T1-weighted MRI. A reference image set was generated that included examples of all lesions and variations in normal anatomy. The first reading exercise assessed reliability on baseline and 2 year scans in 55 patients with AS by 3 readers. Discrep- ant scans were reviewed extensively using radiography as a reference. The second exercise was conducted as follows by the same expert readers on 25 AS patients with baseline/2 year pairs of radiographs and MRI scans: 1. Assessment of radiographs alone. 2. Assessment of MRI scans alone. 3. Assessment of radiographs and MRI scans simultaneously. Reliability was assessed by intra-class correlation coefficient (ICC).

**Results:** ICC for 3 readers reading MRI scans in the first exercise were 0.79 and 0.23 for baseline status and 2 year change scores, respectively. In the second ex- ercise, radiography was superior to MRI in reliably detecting new bone (Table). ICC for detection of new bone in the thoracic spine by MRI was 0.48 and 0.36 for baseline status and 2-year change scores, respectively.

**P83**

**WHAT CONSTITUTES THE CHARACTERISTIC FAT LESION ON MRI OF THE SACROILIAC JOINTS IN EARLY SPONDYLO-ARTHRITIS?**

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**Introduction:** It is well known that fat infiltration (FI) may be observed on T1-weighted MRI in the sacroiliac joints (SII) of healthy and individuals with spondyloarthritis (SpA). We aimed to assess which MRI features might have diagnostic utility in early SpA and in L-spondylosis, respectively.

**Methods:** Cohort A and B comprised 69 and 68 consecutive patients with back pain ≤50 years of age referred from primary care and from orthopaedists with acute anterior uveitis, respectively. They were clinically classified as having non-radio- graphic axial SpA (nr-axSpA) (n=30 and 31 for cohorts A and B, respectively), spondyloarthritis (AS) (n=10 and 24), or mechanical back pain (MBP) (n=39)
and 33). There were 20 healthy volunteers (HV) in cohort A. SIJ T1W MRI were blindly assessed in random order by 4 readers for the following morphological features of FI: distinct border around region of FI, homogeneity of T1W signal, proximity of FI to subchondral bone, and association with other SIJ lesions (bone marrow edema (BME), and erosion (ER)).

**Results:** FI of the SIJ in cohort A/B was recorded by the majority (≥3/4) of readers in 60%/73.9% of AS, in 40%/38.7% of nr-axSpA, in 20.5%/12.1% of MBP, respectively, and in 10% of HV.

**Diagnostic utility (mean of 4 readers for cohort A/B) of SIJ FI in nr-axSpA vs MBP patients**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Sens (mean/SD)</th>
<th>Spec (mean/SD)</th>
<th>LR+ (mean/SD)</th>
<th>LR- (mean/SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FI per se</td>
<td>0.440/0.42</td>
<td>0.730/0.78</td>
<td>1.62/1.91</td>
<td>0.770/0.74</td>
</tr>
<tr>
<td>FI with border</td>
<td>0.210/0.21</td>
<td>0.970/0.90</td>
<td>8.29/2.13</td>
<td>0.830/0.88</td>
</tr>
<tr>
<td>Homogeneous FI</td>
<td>0.200/0.26</td>
<td>0.970/0.93</td>
<td>6.24/3.78</td>
<td>0.830/0.80</td>
</tr>
<tr>
<td>Subchondral FI</td>
<td>0.360/0.35</td>
<td>0.850/0.83</td>
<td>2.36/2.04</td>
<td>0.750/0.78</td>
</tr>
<tr>
<td>FI with any 2 features</td>
<td>0.240/0.30</td>
<td>0.970/0.92</td>
<td>9.26/3.58</td>
<td>0.780/0.77</td>
</tr>
<tr>
<td>FI+BME</td>
<td>0.190/0.18</td>
<td>0.990/0.92</td>
<td>14.63/3.13</td>
<td>0.820/0.90</td>
</tr>
<tr>
<td>FI+ER</td>
<td>0.210/0.24</td>
<td>0.990/0.93</td>
<td>33.15/3.58</td>
<td>0.790/0.81</td>
</tr>
</tbody>
</table>

**Conclusion:** SIJ FI characterized by a distinct border or homogeneity on T1W MRI had substantial diagnostic utility in early SpA. FI in combination with BME or ER also showed high diagnostic utility.

**P85**

**THE SPARCC/SPARTAN (SPAR) REFERENCE IMAGING MOD**

**EIGHT IMMUNOLOGICAL REFERENCE IMAGES (MSASS) FOR CALIBRATION OF READERS SCORING WITH THE MSASS:**

**PRELIMINARY VALIDATION**

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**Introduction:** The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) is used to assess progression in AS but the methodology is not well standardized. In the Spondyloarthritis Research Consortium of Canada (SPARCC) and the Spondyloarthritis Research and Treatment Network (SPARTAN) working group we aimed to develop and validate a reference image module to calibrate readers using the mSASSS.

**Methods:** The working group comprises 5 rheumatologists and 3 musculoskeletal radiologists. We conducted the following: 1. Systematic review of the literature to identify aspects of the mSASSS requiring methodological clarity. 2. Pilot assessment of baseline and 2 year radiographs from 25 patients using the mSASSS. 3. Debriefing of discrepant scores and development of an imaging module with reference images (the SPAR module) which clarifies definitions, rules, and scoring methodology. A follow-up scoring exercise was then conducted by 6 readers on 39 patients with AS, which included 15 from the pilot exercise. Reliability of the mSASSS was assessed by the intraclass correlation method (ICC).

**Results:** The pilot exercise demonstrated excellent reliability for status scores (ICC for 6 readers (range) = 0.92; Median (range) ICC = 0.92 (0.84-0.96)) but poor reliability for change scores (ICC for 6 readers = 0.46; Median (range) for 15 reader pairs = 0.52 (0.11-0.66)). In particular, ICC for change score for the radiologist reading pair was only 0.46. In the follow-up scoring exercise, the ICC for change score for the radiologist reading pair improved substantially to 0.62 although overall reliability for change score for the entire group improved marginally (ICC for 6 readers = 0.49).

**Conclusions:** Reliable assessment of change in mSASSS is very challenging though can be improved for expert readers if they are calibrated according to the standardized methodology in the SPAR module.

**P86**

**SECUKINUMAB REDUCES SPINAL INFLAMMATION AS EARLY AS WEEK 6, AS DETECTED BY MRI – RESULTS OF A DOUBLE-BLIND, PHASE II PROOF-OF-CONCEPT STUDY IN PATIENTS WITH ANKYLOSING SPONDYLITIS**

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**Objectives:** We studied the effects of secukinumab on spinal bone marrow edema as detected by MRI in AS patients.

**Methods:** 30 patients with active AS randomly (4:1) received two i.v. infusions of secukinumab (10mg/kg) or placebo, given 3 weeks apart. Sagittal spinal MR images were performed including T1- and STIR sequences at baseline, wk6 and wk28. Images were analyzed by an independent reader, blinded to treatment allocation and chronology of images, using the Berlin scoring system. Changes in MRI scores between baseline and followup visits were evaluated by Wilcoxon signed-rank test.

**Results:** MRI of 27 patients (22 secukinumab; 5 placebo) were evaluable at baseline. Improvement in MRI scores from baseline with secukinumab was noticed as early as wk6 and sustained up to wk28 (Berlin MRI scores (mean±SD): Baseline: 9.2±4.9; wk6: 6.7±6.6; wk28: 5.7±6.2), especially in patients with higher baseline scores. In contrast, changes in MRI scores were minimal in placebo group.

**Conclusions:** Treatment with only 2 infusions of secukinumab reduces spinal inflammation as detected by MRI in patients with active AS. Improvements in MRI scores were seen as early as 6 wks after start of secukinumab treatment and sustained up to wk28. Results are consistent with MRI findings obtained in previous AS trials with TNF blockers. These results further support the notion that secukinuma- may be a potential treatment for patients with active AS.
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THE BENEFICIAL ROLE OF SPECT/CT IMAGING OVER CONVENTIONAL BONE SCINTIGRAPHY IN THE DIAGNOSIS OF EARLY AXIAL SPONDYLOARTHRITIS

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Background: Imaging is an important tool in diagnosing axial spondyloarthritis (SpA). In contrast to magnetic resonance imaging, conventional bone scintigraphy has been used for the early detection of SpA. However, SPECT (single photon emission computed tomography)/CT has the advantage of better delineating the changes of the sacroiliac joints (SIJ) as well as the underlying structure of the joint. There has been no report studying the use of SPECT/CT in early axial SpA.

Objective: To study the bone SPECT/CT findings of the SIJ in patients with inflammatory back pain yet mild or minimal changes in the SIJ plain radiographs.

Methods: Thirty-three patients (M=8, age 33.2±12.5) presenting with inflammatory back pain were enrolled in a single center (SMG-SNU Boramae Medical Center, BRMC). Patients had mild (grade 1, 2) or no changes in the SIJ plain radiographs.

Bone SPECT/CT was obtained before the second hospital visit. Thirty-three patients that visited the BRMC due to hip joint pain without abnormal findings in plain film or bone scintigraphy were enrolled as controls. We calculated the SIS ratio in the planar scintigraphy image, and measured the uptake in the SIJ using the region of interest (ROI) covering the whole SIJ and sacrum. We also calculated the SIS ratio at the ROI within the bone SPECT/CT image. Mann-Whitney test was used for statistical analysis.

Results: When comparing the SIS ratio of the conventional planar bone scintigraphy, there was no significant difference between the study group and control group (study group: right 1.0±0.24, left 1.0±0.24, range 0.94-1.12 vs. control group: right 1.1±0.34, left 1.0±0.11, range 0.87-1.24). However, the SIS ratio in bone SPECT/CT of study group was significantly higher than control group (study group: right 1.8±0.21, left 1.7±0.28, range 1.4-2.1, control group: right 1.4±0.16, left 1.4±0.15, range 1.04-1.71, p=0.01).

Conclusion: In patients with early changes in SIJ plain radiography, the SIS ratio obtained in bone SPECT/CT and the image itself is more useful than conventional bone scintigraphy in evaluating sacroiliitis. Additional studies will be needed to further investigate the advantages of SPECT/CT in diagnosing early axial SpA.

P88

OVEREXPRESSION OF TOLL-LIKE RECEIVER 2 ON PERIPHERAL BLOOD MONOCYTES FROM PATIENTS WITH PSORIATIC ARTHRITIS (PsA)

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Introduction: Toll-like receptors (TLRs) are highly conserved pattern-recognition receptors (PRRs) that are key triggers of immunity. Ten functional human TLRs have receptors (PRRs) that are key triggers of immunity. Ten functional human TLRs have been identified and they recognize a variety of ligands, including exogenous molecules from invading microbes (pathogen-associated molecular patterns - PAMPs) and endogenous molecules created or up-regulated upon tissue injury (damage-associated molecular patterns - DAMPs). TLR 2 is able to activate innate immune cells in response to gram-positive bacteria, and because gram-positive streptococcus may play a role in PsA, the study of TLR2 regulation in this disease may provide relevant etiopathogenic clues. Thus, we evaluated TLR2 expression on peripheral monocytes and neutrophils from PsA patients, comparing those with active and inactive disease.

Patients and Methods: Forty-five PsA patients with peripheral joint manifestations were studied; disease activity was assessed by DAS 28 score. Control group included 32 sex and age matched healthy subjects. Individuals with infections were excluded. Membrane-bound TLR2 expression was analysed on peripheral blood monocytes and neutrophils by flow cytometry; geometric mean intensity of fluorescence was measured and expressed as median ± interquartile range. Mann-Whitney test was applied to compare differences between groups and p<0.05 considered significant.

Results: Twenty-two PsA patients were male, 23 were females, with mean age ± SD: 51.7±10 years; 10 (27%) were HLA B27+. Twenty-seven had active (DAS28≥3.2) and 18 had inactive PsA. Increased expression of TLR2 was demonstrated on monocytes from patients (89%±17%), both with active (90%±17%) and inactive (88%±17%) PsA compared to healthy controls (71%±49%) (p=0.002, p=0.001 and p=0.04 respectively). In contrast, TLR2 expressions on neutrophils from patients and controls were alike.

Conclusion: Upregulation of TLR2 on monocytes from patients with PsA reinforces the role the innate immune system in the pathogenesis of the disease, possibly through recognition of gram positive microorganisms as trigger or perpetuating agents, independent of clinical active phases of disease.

P90

DELETION OF HLA-B27 T CELLS UNDERLIES THE IMMUNODOMINANT RESPONSE TO INFLUENZA INFECTION ON CLASS I MHC TRANSGENIC MICE

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Introduction: The role of HLA-B27 in modulating host response to infection is undefined, yet has important implications for the mechanism whereby B27 confers susceptibility to arthritis. Despite co-dominant expression of class I MHC (MHC-I) alleles, immune response to viral infections is characterized by a phenomenon called immunodominance (ImDc). The exact mechanisms of ImDc are not clear. Defining factors contributing to ImDc has proved difficult due to multiple MHC-I allele co-expression in humans and normal mice.

Methods: To overcome this limitation, we generated human MHC-I transgenic (TG) mice which are deficient for endogenous mouse MHC-I molecules (i.e., H2-Kb/-Dd, Dk) and express only one human MHC-I allele. To assess whether co-expression of additional MHC-I alleles influences the pattern of anti-flu CTL epitope recognition and ImDc, novel double MHC-I TG mice were established on a DKO background.

Results: In flufected, double TG HLA-A2/B7 or HLA-A2/B27 mice, IFN-γ ELISpot assays with the flu epitopes M1 58-66 (HLA-A2-specific) and NP466-426 (HLA-B7-specific) or NP383-391 (HLA-B27-specific) showed specific recognition of both peptides by both alleles respectively. In contrast, in influfected HLA-B7/ B27 Tg mice a significantly reduced NP383-restricted CTL response was detected while there was no change in the response level of NP418-restricted CTL. Subsequent fluf-specific studies revealed that co-expression of B7 and B27 is associated with i) a partial deletion of Vβ12+B7/TP383-restricted CD8+ T cells and ii) a failure of Vβ12+CD8+ T cell expansion following flu infection in B7/B27 Tg mice. Using chimeric mice, we confirmed that the lower number of naive B27-restricted CD8+ T cells in B7/B27 Tg mice, compared to single Tg B27 mice, is due to negative selection of B27-restricted Vβ12+CD8+ T cells.

Conclusions: The pattern of allele co-expression critically influences the flu CTL response. The selective deletion of B27-restricted T cells has important implications for models defining the role that HLA-B27 plays in susceptibility to reactive arthritis and ankylosing spondylitis.
**P91**

**FC GAMMA RECEPTORS IN ACTIVE PSORIATIC ARTHRITIS (PSA)**

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**Introduction:** FC receptors for IgG play important roles in collagen-induced arthritis. Monocytes are precursors of tissue macrophages and osteoclasts, two cell types that contribute to destructive processes in arthritis. In the circulation different monocyte subsets with unclear functions have been detected, they express FC receptors. We wanted to study monocyte subsets and monocytic FC receptor status in active PSA.

**Materials and Methods:** 23 polycellular PSA patients with active joint disease (mean DAS28=4.1; mean HAQ=0.77; mean PASI=4.1; mean CRP=12.3) and 33 healthy controls, age and gender matched, were included in the Rheumatology department/Academiska University Hospital. Monocyte subsets were defined upon their expressions of CD14 and CD16. For FC receptor expressions flow cytometry, for immune complex binding a rosetting technique and for IgG-stimulated TNF-production a sandwich ELISA were done. For statistics the Mann-Whitney U-test and the Spearman correlation test were used.

**Results:** In active PSA the numbers of CD14+ monocytes are similar to healthy controls but the monocytic subpopulation CD14++CD16+ is increased. A raise in IgG-subclasses (1-3) is seen in the patient population. The frequency of CD64 positive monocytes is increased; this receptor is occupied with more endogenous IgG than in healthy controls. FC receptor expressions correlate with some independent markers for disease activity. The FC gamma receptor function is not significantly affected although we see a trend of less IgG-stimulated TNF-production in patients on DMDARD-therapy. FC gamma receptor functions correlate with disease activity.

**Conclusions:** Innate and humoral immunity are activated in PSA. With ongoing joint inflammation the CD14++CD16+ subpopulation increases, probably as a result of increased load of IgG and/or immune complexes in the circulation. Especially CD64 (FC gamma receptor I) seems to play an important role in PSA. CD64 and monocytic cell surface bound IgG may serve as markers for active joint disease. Our findings seem to relate to joint inflammation and not to skin inflammation in PSA.

**P92**

**TH17 CELLS EXPRESSING KIR3DL2 AND ENRICHED FOR GUT HOMING MARKERS ARE INCREASED IN ANKYLOSING SPONDYLITIS**

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**Introduction:** Th17 helper T (Th17) cells are a subset of pro-inflammatory CD4+ T cells implicated in a number of inflammatory arthritides including the Spondyloarthritides (SpA). Ankylosing Spondylitis (AS), the commonest spondyloarthrophy, is genetically associated with HLA-B27 (B27) and IL-23 receptor polymorphisms, however the link remains unexplained. We have previously shown KIR3DL2+ CD4+ T cells are expanded in the peripheral blood of individuals with AS.

**Aim:** The aim of the study was to further characterise KIR3DL2+ CD4+ T cells and to investigate whether activation increased or induced expression of KIR3DL2 on CD4+ T cells.

**Methods:** KIR3DL2+ CD4+ T cell phenotype was investigated by flow cytometry. Production of cytokines by PMA/ionomycin stimulated-PBMCs was investigated by intracellular cytokine staining (ICS). Cytokine production by nCD3/28-stimulated FACS-sorted KIR3DL2+ and KIR3DL2- CD4+ T cells was investigated by multiplex bead analysis. Expression of KIR3DL2 on CD4+ T cells was investigated after SEB stimulation and cytokine production was investigated by ELISA.

**Results:** KIR3DL2+ CD4+ T cells, increased in peripheral blood of HLA-B27+ SpA patients, were enriched for expression of Th17 phenotypic markers, IL-23R, CCR6 and IL-1R, and the gut-homing chemokine receptor, CCR9. KIR3DL2+ CD4+ T cells from AS patients produced significantly more IL-17 than KIR3DL2- CD4+ T cells. IL-17 levels significantly increased in the presence of the Th17 cytokines Rantes and IL-1. SEB activation increased the number of KIR3DL2+ cells and IL-17 production more in AS patients than controls.

**Conclusions:** KIR3DL2+ CD4+ Th17 cells are expanded in patients with Spondyloarthritis. Expression of KIR3DL2 on CD4+ T cells can be induced by activation. These cells constitute a significant proportion of peripheral blood CD4+ TIL-23R-expressing cells and produce increased levels of IL-17, which is further increased by the presence of Th17 cytokines. Our findings will support the trial of new therapeutic strategies, such as anti-IL-17 in AS/SpA.
ELEVATED SOLUBLE E-CADHERIN LEVELS IN CHRONICALLY INFLAMED JOINTS FAVOUR TNF PRODUCTION BY KLRG1 EXPRESSING T CELLS
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Introduction: The killer cell lectin-like receptor G1 (KLRG1) is a NK cell marker that is also expressed on antigen-experienced T cells showing an immune senescent phenotype. KLRG1 binding to its ligand E-cadherin results in inhibition of cytokine-producing and cytotoxic T cell responses. Recently, the soluble form of E-cadherin (sE-cadherin) has been shown to influence KLRG1 signaling. Furthermore, it has been hypothesized that senescent T cells play a role in development of autoimmunity but the potential involvement of KLRG1 in an arthritic/rheumatic disease has not been investigated yet.

Patients and Methods: PBMC/SEMC from 21 chronic arthritis patients (rheumatoid arthritis (RA) or spondyloarthritis (SpA)), 8 patients with crystal induced acute arthritis (gout and chondrocalcinosis) and 10 healthy controls were obtained. T cells were characterized for KLRG1 expression directly ex vivo, while TNF/IFN-γ-production was assessed after 4h PMA/CaI stimulation by flow cytometry. In addition, sE-cadherin levels in paired plasma – SF were determined. Moreover, TNF/IFN-γ production by T cells was compared in the presence/absence of sE-cadherin in a 7-day co-culture system.

Results: More T cells were KLRG1+ in the SF as opposed to the PB of patients with chronic arthritis (RA and SpA), which contrasts strikingly with results obtained in crystal induced arthritides. The KLRG1+ T cell subset had a functionally more active phenotype, characterized by increased capacity to produce proinflammatory cytokines such as TNF or IFN-γ. Levels of sE-cadherin were found to be markedly higher in the SF of all arthritides. Unexpectedly, the presence of sE-cadherin enhanced TNF but not IFN-γ production by KLRG1+ T cells. Importantly, this pathway seems to be operational in both RA and SpA, but not in acute crystal induced forms of arthritis.

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DISCOVERY OF TWO PUBLIC T CELL RECEPTOR CLONOTYPES IN B27+ ANKYLOSING SPONDYLITIS BY DEEP REPOIRE SEQUENCE ANALYSIS
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Background: The strong association of AS with HLA-B27 implicates a T cell immune receptor. However, the specific T cell receptor (TcR) clonotypes would be shared among AS patients.

Methods: We have developed a technology for large scale sequencing of TcR to assess the repertoire profile. All TcR sequences are amplified from peripheral blood and ~1 million TcR sequences are obtained to generate a comprehensive profile of TcR repertoire. We applied this technology to profile B27+ AS (n=128), B27- AS (n=24), B27-: mechanical back pain (n=24), healthy controls (n=25) and SLE patients (n=176).

Results: We used a TcR repertoire data from the controls (HC and SLE) to filter out clonotypes present in an appreciable number of these samples. After rigorous control of multiple testing using train and test data sets, two clonotypes were discovered to have significantly different frequencies in B27+ AS population and controls (41% vs 5% and 54% vs 19%, p<0.0001). These clones were further tested in 24 patients with mechanical back pain and 24 B27- AS patients. The frequency of both clonotypes in the MBP population was similar to that in controls (4% vs 5% and 5% vs 25% vs 19%). In B27- AS one clonotype had frequency similar to controls (8% vs 5%), and one had a higher frequency than controls (42% vs 25% p=0.016). The table below shows the frequency of both clonotypes in the different populations.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>Clone 1: no. positive (%)</th>
<th>Clone 2: no. positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B27+ AS</td>
<td>128</td>
<td>54 (41%)</td>
<td>69 (54%)</td>
</tr>
<tr>
<td>B27- AS</td>
<td>24</td>
<td>2 (8%)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td>MBP</td>
<td>24</td>
<td>1 (4%)</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>Controls</td>
<td>201</td>
<td>11 (5%)</td>
<td>38 (19%)</td>
</tr>
</tbody>
</table>

Conclusion: We provide evidence that there is a distinctive set of shared clonotypes in the T cell repertoire in AS patients. These clonotypes provide a useful tool for the immunology of HLA B27 in AS and demonstrates promising specificity for potential diagnostic utility.

KIR3DL2 BINDS TO HLA-B27 DIMERS AND FREE HEAVY CHAINS MORE STRONGLY THAN OTHER HLA CLASS 1 AND PROMOTES THE EXPANSION OF PATHOGENIC NK AND T CELLS IN SPONDYLOARTHITIS
Wong-Baeza I.1, Ridley A.1, Shaw J.1, Hatano H.1, Piper C.1, McHugh K.1, Bowness P.1, Kolbberger S.1
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Background: HLA-B27 (B27) is expressed at the cell surface as classical [2m-associated B27, diisulphide-bonded heavy chain homodimers (termed B272)] and other free heavy chain forms (FHC). B272, but not classical B27 binds the killer cell immunoglobulin-like receptor KIR3DL2. CD4 T cells expressing KIR3DL2 and highly enriched for expression of Th17 markers such as IL23R are expanded in spondyloarthritides (SpA) patients. KIR3DL2-expressing CD4 T cells produce high amounts of IL17 and other inflammatory cytokines in SpA. KIR3DL2 also binds HLA-A3 and -A11 which are not associated with SpA. Stronger interactions of B272 and B27 FHC with KIR3DL2 compared to other HLA class I could promote the expansion of proinflammatory KIR3DL2+ leukocytes in SpA. Thus we compared the strength of interaction of KIR3DL2 with B27 and effects on cell function with other HLA class 1.

Methods: Class 1 tetramer interactions with KIR3DL2 and KIR3DL2Fc binding to different HLA class 1 were investigated by FACs staining of transfected and primed primary cell lines. We studied activation and survival of KIR3DL2-expressing leukocytes in flow cytometry (flow cytometry). We performed experiments with KIR3DL2Fc-expressing reporter cells stimulated with different HLA class 1. We compared proliferation, survival and cytokine production of KIR3DL2+ T cells from SpA patients and control peripheral blood mononuclear cells (PBMC) or cells stimulated with antigen-presenting cells (APC) expressing B27, or control HLA class I by FACs and ELISA assay.

Results: B272 tetramers bound more strongly to KIR3DL2 than HLA-A3 and other HLA class 1. KIR3DL2Fc bound HLA-B27 more strongly than HLA-A3 and control HLA class 1. KIR3DL2-expressing leukocytes stimulated with B272, expressing APC survived better than cells stimulated with control HLA class 1. B27 dimers and HFC stimulated greater production of IL-2 by KIR3DL2Fc-expressing reporter T cells compared to stimulation with control class 1 (resting 15.0±2pg/ml; +B272, 813±54pg/ml; +HLA-A3 192±49pg/ml; HLA-B27 65±3pg/ml; mean±SD). Peripheral blood KIR3DL2 expressing T cells expanded more than T cells from controls in response to antigen stimulation by syngeneic APC.

Discussion: The enhanced survival of KIR3DL2-expressing leukocytes in SpA patients could result from increased avidity of interaction with B272 and B27 FHC compared to other HLA class I ligands. B27-KIR3DL2 interactions could promote expansion of proinflammatory NK and Th17 cells in disease.

HLA-B*2709 FORMS LESS CELL SURFACE B27 DIMER AND FREE HEAVY CHAIN LIGANDS FOR KIR3DL2 AND LILRB2 IMMUNORECEPTORS THAN ARTHRITIS-ASSOCIATED HLA-B*2705
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Objectives: We hypothesised that differential interactions with KIR and LILIR immunoreceptors could contribute to the association of HLA-B*2705 and lack of association of HLA-B*2709 with ankylosing spondylitis (AS). HLA-B*2705 heavy chain dimers (B272) and β2m-associated heterotrimers bind KIR3DL1 and LILRB2 receptors. By contrast only HLA-B*2705 dimers bind KIR3DL2. Thus, we compared formation of β2m-free heavy chains (FHC) including B272, by HLA-B*2705 and -B*2709 and their interaction with KIR and LILIR.

Methods: We studied formation of HLA-B*2705 and HLA-B*2709 heterotrimers and FHC forms in vitro and in transfected cells. We studied HLA-B*2705 and -B*2709 interactions with KIR3DL1, KIR3DL2 and LILRB2 by FACs staining with class 1 tetramers, LILRB2Fc and KIR3DL2Fc proteins and using KIR3DL2 and LILRB2 reporter cells and KIR3DL2-expressing NK and T cells. We measured KIR expression on peripheral NK and CD4 T cells from 18 HLA-B*2705 AS patients, 8 HLA-B27 negative and 12 HLA-B*2705+ and HLA-B*2709+ healthy controls by FACs staining.

Results: HLA-B*2709 formed less B272 and FHC than HLA-B*2705. HLA-B*2705 stimulated KIR3DL2CD3e-reporter T cells more and stained more strongly with LILRB2Fc than HLA-B*2709. HLA-B*2705 promoted KIR3DL2+ leuko-
cyte cell survival more strongly than HLA-B*2709. HLA-B*2705 and -B*2709 dimer tetramers stained KIR3DL1, KIR3DL2 and LILRB2 equivalently. Increased proportions of NK and CD4 T cells expressed KIR3DL2 in HLA-B*2705+ AS patients compared to HLA-B*2705+ -B*2709+ and HLA-B27- healthy controls. 

**Conclusions:** Differences in the formation of FHC ligands for KIR3DL2 and LILRB2 by HLA-B*2705 and -B*2709 could contribute to the differential association of these alleles with AS.

**P99**

**SYNOVIAL FLUID DERIVED INKT CELLS IN CHRONIC ARTHRITIDES SHOW AN INCREASED PROGRAMMED DEATH-1 EXPRESSION AND ANERGIC PHENOTYPE**

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**Introduction:** Invariant Natural Killer T (iNKT) cells recognize glycolipids presented by CD1d on Antigen Presenting Cells and have the capacity to secrete copious amounts of cytokines. Earlier work demonstrated the regulatory capacity of iNKT cells in a murine model for spondyloarthritis (SpA) but little is known of these cells in arthritis patients. In this study, we aimed to evaluate the iNKT cell frequency, phenotype and glycolipid reactivity in the peripheral blood (PB) and synovial fluid (SF) in arthritides.

**Patients and Methods:** We obtained blood and paired SF of 18 SpA and 16 rheumatoid arthritis (RA) patients (chronic arthritis), 10 patients with gouty arthritis (acute arthritis) and 20 healthy controls (HC; only PB). PB and SF mononuclear cells (MC) were isolated by density centrifugation and analyzed by flow cytometry. To test iNKT cell reactivity, PBMC and SFMC were cultured in the presence of α-GalactosylCeramide (α-GalCer, a prototypical iNKT ligand) or the bacterial diacylglycerol B6GGLII (from Borellia burgdorferi) and Pl-105 (Streptococcus pneumoniae).

**Results:** Although a reduced frequency of iNKT cells was observed in PB of SpA and RA patients as compared to HC, iNKT cell numbers were significantly enriched in SF of these chronic arthritis patients, whereas this was not seen for gouty patients. Phenotypical analyses indicated that an increased number of SF iNKT cells of patients with SpA and RA (but not gouty arthritis) significantly expressed Programmed Death-1 (PD-1), a co-inhibitory receptor linked to iNKT cell anergy. Consistently, α-GalCer induced iNKT cell expansion in SFMC was weaker as compared to paired PBMC. Moreover, SFMC showed increased responses towards α-GalCer in the presence of PD-1 neutralizing antibodies. Remarkably, in some patients, SF opposed to PB iNKT cells responded towards bacterial iNKT ligands.

**Conclusions:** Our data suggest a disease associated mechanism of iNKT cell activation in the inflamed joint of chronic but not acute forms of arthritis.

**P100**

**IMMUNOGLOBULIN SUBCLASS ANALYSIS INankylosing Spondylitis**

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**Background:** Recent experience with extra-articular manifestations of AS has included retropertional fibrosis, but it has not been addressed whether AS may be part of the IgG4 disease spectrum or whether IgG subclasses in AS are abnormal.

**Objectives:** To study IgG subclass profiles in AS and analyze clinical-serological correlations in these patients.

**Methods:** Serum levels of IgG subclasses were analyzed in 105 serial patients in the AS clinic. There were 83 males, 22 females with a mean age of 41.8 yr. 68 patients were HLA-B27+.

**Results:** Contrary to expectations, IgG2 demonstrated the most frequent abnormalities in AS. The table depicts some of the clinical correlations observed. IgG2 revealed a correlation with IgG4 (r= 0.30, p=0.002) but no correlation with CRP or ESR.

**Conclusions:** IgG2 subclass analysis in AS revealed that the IgG2 was the commonest subclass abnormality. The correlation with the presence of iritis and IBD suggests this test may have utility in identifying AS patients with particular extra-articular features of the disease.

__Poster Presentations__

**Eighth International Congress on Spondyloarthritis**

<table>
<thead>
<tr>
<th>IgG2 analysis in AS</th>
<th>Frequency (%) or Mean (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>38.8 (14.1) - 42.3 (13.8)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>12/3 - 7/19 NS</td>
</tr>
<tr>
<td>Age at onset of AS</td>
<td>20.3 (11.4) - 23.8 (9.9)</td>
</tr>
<tr>
<td>Age at diagnosis of AS</td>
<td>21.4 (9.7) - 51.7 (12.9)</td>
</tr>
<tr>
<td>HLA B27</td>
<td>9 (75.0%) - 59 (71.1%) NS</td>
</tr>
<tr>
<td>Iritis</td>
<td>7 (53.9%) - 18 (20.2%) 0.01</td>
</tr>
<tr>
<td>Psoiriatis vulgaris</td>
<td>2 (15.4%) - 0 (3.5%) 0.13</td>
</tr>
<tr>
<td>BiD</td>
<td>4 (30.8%) - 7 (7.9%) 0.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (15.4%) - 4 (4.5%) 0.17</td>
</tr>
<tr>
<td>BasDAI score</td>
<td>1.8 (1.2) - 3.6 (2.5) 0.05</td>
</tr>
</tbody>
</table>

**P101**

**EXPRESSSION OF HLA-B27 HEAVY CHAIN FORMS IN ANKLYLOSING SPONDYLITIS AND HLA-B27 POSITIVE CELL LINES**

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**Background:** The strong association of human leukocyte antigen HLA-B27 with a group of spondyloarthopathies (SpA), particularly with Ankylosing Spondylitis (AS), led our research group to the discovery of B27 heavy chain dimer/multimer formation. We proposed that these unique molecules may influence immune homeostasis and cause the disease onset. Investigation of the cell surface expression patterns of the distinctive forms of HLA-B27 heavy chains under different environmental conditions on patient APCs or HLA-B27 positive cell lines will help us to understand disease mechanisms.

**Methods:** HD6 antibody (Ab) was generated by phage display technology. Primary HD6 (HLA-B27 heavy chain dimer specific) and HD10 (heavy chain specific) unconjugated Abs along with control Abs (ME-1, W6/32) were used to determine cell surface expression levels and patterns of different forms of MHC class I molecules in the steady state and under different environmental conditions (e.g. LPS treatment, brief low pH exposure) by flow cytometry, confocal microscopy and protein immunoprecipitation. We studied HLA-B27 transduced/non-transduced human B cell lines LBL721.220 (.220) and LBL721.221 (.221) and AS patient and control peripheral mononuclear blood cells (PBMC) and monocyte derived dendritic cells. HLA-B27 transduced/positive or control cells were stained with primary HD6, ME-1, W6/32 or isotype control mAb and secondary anti-mouse fluorochrome conjugated (Alexa Fluor 633) antibody in all flow cytometry and confocal microscopy experiments.

**Results:** Flow cytometry demonstrated increased heavy chain expression on the cell surface of AS patient moDCs compared with healthy controls. Moreover, patient dendritic cells after LPS stimulation and under stress conditions enhance cell surface expression of heavy chain forms. Immunoprecipitation of cell surface proteins from HLA-B27-transduced cell lines confirmed our dendritic cell data. Confocal microscopy demonstrated distinct heavy chain expression patterns on the .221 HLA-B27 cells and a similar tendency to significantly increase levels of HC10 and HD6 reactive molecules on the cell surface after low pH treatment.

**Conclusions:** Cell surface expression of HLA-B27 heavy chain forms can be demonstrated using a variety of techniques and could be one factor contributing to AS pathogenesis.

**P102**

**DIRECT IDENTIFICATION OF ENDOSGENOUSLY PROCESSED HLA-B27-RESTRICTED EPITOPES FROM CHLAMYDIA TRACHOMATIS USING LC-MS/MS**

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**Introduction:** The spondyloarthopathies are a group of rheumatic diseases that include ankylosing spondylitis (AS) and reactive arthritis (ReA), and are strongly
associated with HLA-B27. Although this association is among the strongest between an HLA antigen and any disease, the pathogenic mechanism remains unknown. ReA can be triggered by diverse bacteria, one of the most prominent is Chlamydia trachomatis. Several epitopes derived from chlamydial proteins have been identified using CTL recognition in vitro and epitope mapping in silico, but direct identification of chlamydial epitopes in vivo is much more elusive. The purpose of this study was to directly identify Chlamydia-derived HLA-B27 ligands processed and presented in vivo, and to examine their potential as mediators of molecular mimicry.

Methods: A new methodology is described for studying the internal processing and presentation of several immunogenic epitopes. This includes stable transfection of the bacterial protein and purification of the peptide-MHC complexes from the surface of HLA-B27-positive cells, followed by high-throughput comparative peptide sequencing. A second targeted search was used for detecting specific peptides within the HLA-B27 peptidome.

Results: The use of broad-spectrum techniques with high resolution and sensitivity allowed us to detect peptides derived from the bacterial CspC (CT286), DNA primase (C794) and NQRA (CT634) proteins. These peptides showed high homology to human protein sequences and might be candidates for molecular mimicry.

Conclusions: This study provides direct evidence that multiple chlamydial proteins can be processed in vivo and presented at the cell surface in the context of HLA-B27. The high-resolution and sensitivity of cutting-edge MS techniques provide a major improvement in the detection of Chlamydia-derived peptides with putative pathogenic relevance.
P106
METALLOPROTEINASE-3 (MMP-3) IS A PREDICTOR FOR ANTI-TNF-α RESPONSE IN PATIENTS WITH ANKYLOSING SPONDYLITIS (AS)
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Introduction: Better objective measures for evaluating disease activity and to predict anti-TNF-α response in patients with AS are necessary. MMP-3 seems to be the most promising biomarker although published data are not conclusive.

Objectives: To evaluate the change of MMP-3, dkk-1 and sclerostin serum levels after anti-TNF-α therapy, and to investigate their correlation with disease activity and their utility to predict anti-TNF-α response in patients with AS.

Methods: Patients with AS who initiated anti-TNF-α therapy were included (November 2010-July 2011). Before and after 3 months of therapy, disease activity (BASDAI, ASDAS and CRP) was measured, and blood samples were collected to determine serum levels of MMP-3, DKK-1 and sclerostin by enzymoimmunoanalysis. Biomarkers change was compared in responders versus non-responders, based on BASDAI50 and ASDAS response (Mann-Whitney U test). Accuracy to predict response (ROC analysis) and correlation testing were performed.

Results: Twenty AS patients were included; 80% received adalimumab and 20% received etanercept. Median age and disease duration were 42.4 and 6.8 years, respectively; 86% was men, and 83% HLA-B27 positive. After 3 months of anti-TNF-α, all disease activity parameters improved significantly. MMP-3 levels decreased (100.0 vs 68.1 ng/ml; p<0.05) while DKK-1 and sclerostin levels did not change significantly (7.07 vs 6.57 pmol/l; p=0.5 and 21.7 vs 22.7 pmol/l; p=0.5, respectively). Moreover, MMP-3 decreased only in responders to anti-TNF-α (Table 1). Baseline biomarker levels were significantly different between responders and non-responders only for MMP-3 (122.9 vs 58.9 ng/ml; p=0.05, respectively). The AUC for MMP-3 to predict BASDAI50 and ASDAS response was 0.73 and 0.78, respectively. The best cut-off was for levels ≥ 59.5 ng/ml, with sensitivity 79-85% and specificity 50-57%. The only correlation observed between biomarkers and disease activity parameters was between MMP-3 and pain VAS.

Conclusions: Serum MMP-3 decreased after anti-TNF-α therapy. MMP-3 levels are useful to predict response to anti-TNF-α, but are not correlated with disease activity in AS patients.

Table I. Change in serum levels of MMP-3, DKK-1, sclerostin and CRP after 3 months of anti-TNF-α therapy based on the clinical response.

<table>
<thead>
<tr>
<th></th>
<th>Responders N=11 (65%)</th>
<th>Non-responders N=7 (35%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 months</td>
</tr>
<tr>
<td>MMP-3 (ng/dl)</td>
<td>122.2</td>
<td>64.1</td>
</tr>
<tr>
<td>DKK-1 (ng/dl)</td>
<td>6.9</td>
<td>8.1</td>
</tr>
<tr>
<td>SCL (pmol/l)</td>
<td>23.6</td>
<td>23.4</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>16.3</td>
<td>4.0</td>
</tr>
</tbody>
</table>

P107
CLINICAL EFFICACY AND SAFETY OF INFliximab – RESULTS AFTER A DECADE OF CONTINUOUS TREATMENT IN ANKYLOSING SPONDYLITIS
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Introduction/Aim: The efficacy of anti-TNF in patients with active AS has been established for longer-term periods. This is the final report of the first clinical trial with infliximab in patients with initially active AS.

Methods: At the start of the PCP of the study (baseline, BL), all patients (n=69) had active disease (BASDAI and spinal pain ≥ 4). After 3 months, all patients continued to receive infliximab 5mg/kg i.v.6 weeks in an OLE phase of the study and were assessed regular intervals. All results are described on the basis of a completer analysis.

Results: While 42 patients were still in the study at 5y (60.9%), 29 (42.2%) reached 10y. At 10y, the mean ASDAS was 1.7±1.0 (BL: 4.3±0.8, p<0.001). Similarly, all other parameters remained in low levels. ASDAS inactive disease status was reached by 12/29 (41.4%) patients but only 5 patients showed ASAS partial remission (PR) (17.2%). This difference was due to 6/24 patients not in ASAS-PR (25%) who had scores <2 in 3/4 remission parameters and a score ≥2 in only 1 parameter: BASFI (n=4) and patient’s global assessment (n=2).

There were no differences in BL status scores between completers and patients who had dropped out. At the last available assessment time point, the mean BASDAS was 3.9±2.1 for drop outs vs 2.7±2.0 for completers. Overall, 40 patients dropped out of the study but only 23 (57.5%) due to AEs. Infusion reactions gave reason to discontinue in 3 patients.

Conclusions: The efficacy of infliximab lasted over 10 years – in those 29 patients who had remained in the study. There was no indication of a loss of efficacy. The most frequent reason for treatment discontinuation were AEs and pragmatic reasons. Lack of efficacy and infusion reactions contributed to only 15% of all drop outs (<10% of patients). There was no new safety signal in this small prospective study over 10y.

P108
LONG-TERM OUTCOME OF PATIENTS WITH ACTIVE ANKYLOSING SPONDYLITIS WITH ENTAnercept – SUSTAINED EFFICACY AND SAFETY AFTER 7 YEARS
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Introduction/Aim: Data from clinical studies on the long-term efficacy and safety of anti-tumor necrosis factor (TNF)-α therapy in patients with ankylosing spondylitis (AS) are scarce.

Objectives: This is the first report on continuous treatment with the TNF-α fusion protein etanercept over 7 years (y).

Methods: Overall, 26 patients with active AS were initially treated with etanercept 2x25mg s.c. week with no concomitant DMARPS or steroids. The clinical response was assessed by standardized parameters. The primary outcome was the proportion of patients in ASAS partial remission at 7y. ASDAS scores for status and improvement were compared to conventional outcome measures.

Results: Overall, 21/26 patients (81%) completed 2y and 16/26 patients (62%) completed 7y. In the completer analysis, 31% patients were in ASAS clinical remission at 7y, while 44% patients showed ASDAS inactive disease status. Mean ASDAS scores which were elevated at baseline (6.3±0.9) showed constant improvement and remained low: 3.1±2.5 at 2y and 2.5±2.2 at 7y, while ASDAS also improved (3.9±0.7 at baseline, 1.8±0.9 at 2y, 1.6±0.8 at 7y), all p<0.001. From the 10 dropouts, only 5 patients discontinued treatment due to adverse events. Patients who completed the study had lower baseline BASFI scores vs. patients who discontinued. No other clinical parameter at baseline could predict any long-term outcome.

Conclusions: This study confirms the clinical efficacy and safety of etanercept in patients with active AS over 7y of continuous treatment. After 7y, more than half of the initially treated patients remained on anti-TNF therapy, and 1/3 were in partial remission.

P109
DISEASE BURDEN IS COMPARABLE IN NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS AND ANKLOYSING SPONDYLITIS PATIENTS: TREATMENT IMPLICATIONS
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Introduction/Aim: To compare disease characteristics of non-radiographic axial SpA (nr-axSpA) and ankylosing spondylitis (AS) patients from registries and randomized clinical trials (RCTs) with adalimumab.

Methods: Registries [German SpA Inception Cohort (GESPIC) and Kitzb] included both patients with AS and nr-axSpA. Adalimumab RCTs included the ATLAS study in AS, and the ABILITY-1 and Habel studies in nr-axSpA. RCT patients had pre-specified levels of disease and inadequate response to NSAIDs.

Results: Mean age was similar but there were more female nr-axSpA patients compared with AS. Similar levels of disease activity were seen between nr-axSpA and AS (Table).
### P110

#### SUSTAINED EFFICACY OF ADALIMUMAB IN NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS: WEEK 68 RESULTS FROM ABILITY 1

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Charité Universitätsmedizin, Berlin, Germany; Leiden University Medical Center, Leiden, The Netherlands; Hospital Cochin, Paris, France; Ghent University Hospital, Ghent, Belgium; CHU de Tours, Hôpital Trousseau, Tours, France; Abbott, Abbott Park, USA

Introduction/Aim: Adalimumab (ADA) reduced the signs and symptoms of non-radiographic axial spondyloarthritis (nr-axSpA) at week 12. This post-hoc analysis explored long-term efficacy and safety of ADA in patients with nr-axSpA.

Methods: ABILITY-1 is an ongoing double-blind, randomized, controlled trial in nr-axSpA patients (fulfilling ASAS axial SpA criteria but not modified New York criteria for AS) who had an inadequate response, intolerance, or contraindication to NSAIDs. The 12-week, double-blind period was followed by an open-label extension for up to 144 weeks. Clinical responses at week 68 were summarized by observed and non-responder imputation (NRI) analyses.

Results: 144 patients had data available for the week 68 analysis (69/91 from ADA, 75/94 from original placebo). Efficacy is sustained with long-term ADA therapy up to 144 weeks. Clinical responses at week 68 (Table): 58.0% ASAS20, 40.4% ASAS40, and 27.9% ASAS50. The primary endpoint was the proportion of subjects meeting ASAS partial remission criteria at week 28. ASAS-20 and ASAS-40 responses were also observed and non-responder imputation (NRI) analyses.

Conclusion: Treatment with adalimumab during 2 years indicated a down-regulatory effect on both osteoblasts and osteoclasts and resulted in a large increase in BMD in lumbar spine and total hip in osteoporotic AS patients.

<table>
<thead>
<tr>
<th>Week 68 Clinical Responses</th>
<th>Completers(n=144)</th>
<th>Any ADA(n=183)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASAS20</td>
<td>80</td>
<td>63</td>
</tr>
<tr>
<td>ASAS40</td>
<td>67</td>
<td>52</td>
</tr>
<tr>
<td>ASAS50</td>
<td>49</td>
<td>39</td>
</tr>
<tr>
<td>ASAS partial remission</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>ASDAS inactive disease</td>
<td>47</td>
<td>37</td>
</tr>
<tr>
<td>BASDAI50</td>
<td>65</td>
<td>51</td>
</tr>
</tbody>
</table>

### P111

#### INCREASE IN BONE MINERAL DENSITY AND DECREASE IN WNT3A, OPG, CTX-I AND OSTEOCALCIN IN ANKYLOSING SPONDYLITIS TREATED WITH ALENDRONATE

Forsblad-d’Elia H., Narkula M., Zetterberg K., Klingberg E., Carlsten H.
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Introduction and Aims: Ankylosing spondylitis (AS) is associated with increased prevalence of osteoporosis and vertebral fractures and also with enhanced pathological new bone formation resulting in syndesmophyte formation in spine. The knowledge of pharmacological treatment of osteoporosis in AS is limited. The aims were to investigate the effects of adalimumab, 70 mg once weekly, and a daily dose of 500-1000 mg calcium and 400-800 IE vitamin D3 on BMD and biomarkers of bone metabolism in a 2-year non-controlled prospective trial.

Patients and Methods: AS patients with BMD < 2.5 SD, T-score in lumbar spine and/ or hip alternatively BMD < -2.0 SD in addition to at least one fragility fracture were included. Patients were investigated by DXA at baseline and annually thereafter. Blood samples were obtained at baseline, after 1, 3, 6, 12, 18 and 24 months in the morning after an overnight fast. Serum levels of the biomarkers Wingless proteins (Wnt3a), Dickkopf-1 (Dkk-1), sclerostin, soluble receptor activator of nucleotide co-receptors B7 (sRANKL), osteoprotegerin (OPG), degradation product of C-terminal telopeptides of Type-I collagen (CTX-I) and osteocalcin were measured by ELISA.

Results: Sixteen patients (50% women), mean age 56.1±12.8 years, disease duration 18.7±11.4 years, median BASDAI score 4.2 (1.3-8.1) and BASMI 4.4 (1.0-6.6) were included. BMD increased by 9.6±7.5 % (p=0.003) in lumbar spine, 3.0±3.3 % (p=0.016) in total hip and by 4.2±13.5 % (NS) in distal radius. Wnt3a decreased from median 3.88 range (2.93-6.21) ng/ml to 1.74 (1.08-2.84) ng/ml (p<0.001). OPG from 4.07 (2.08-7.78) pmol/l to 3.06 (1.35-4.54) (p<0.001). CTX-I from 0.50 (0.16-1.34) ng/ml to 0.18 (0.07-0.41) ng/ml (p=0.001) and osteocalcin decreased from 20.11 (11.55-59.78) ng/ml to 7.94 (5.63-14.13) ng/ml (p<0.001). Conclusion: Treatment with adalimumab during 2 years indicated a down-regulatory effect on both osteoblasts and osteoclasts and resulted in a large increase in BMD in lumbar spine and total hip in osteoporotic AS patients.

### Poster Presentations

#### P111

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ly greater percentages of patients in the IFX+NPX group than in the PBO+NPX group (Table I).

Table I. Patients with partial remission, response, and absence of MRI lesions at Week 28.

<table>
<thead>
<tr>
<th></th>
<th>IFX+NPX (n=105)</th>
<th>PBO+NPX (n=51)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASAS partial remission</td>
<td>65 (61.9)</td>
<td>18 (35.3)</td>
<td>0.0021</td>
</tr>
<tr>
<td>ASAS-40 response</td>
<td>79 (75.2)</td>
<td>29 (56.9)</td>
<td>0.0263</td>
</tr>
<tr>
<td>ASAS-20 response</td>
<td>85 (81.0)</td>
<td>37 (72.5)</td>
<td>0.3011</td>
</tr>
</tbody>
</table>

Conclusions: 62% of patients with early, active axial SpA reached clinical remission with IFX+NPX vs 35% with NPX alone; clear superiority of combination therapy over NPX monotherapy was also evident for ASAS-40, but not ASAS-20, response. MRI remission was achieved with combination treatment but not NPX alone. The safety profile was consistent with that of other anti-TNF biologics.

P113

A RANDOMIZED, OPEN-LABEL STUDY TO EXPLORE WHETHER PARTIAL REMISSION CAN BE MAINTAINED WITH NAPROXEN OR NO TREATMENT IN PATIENTS WITH EARLY, ACTIVE AXIAL SPONDYLOARTHRITIS: INFAST PART II


Background: In patients with axial spondylarthropathy (SpA) who have achieved partial remission, it is unclear whether continuous treatment with NSAIDs is superior to stopping treatment.

Objectives: To investigate whether continued treatment with naproxen (NPX) was superior to discontinuing all treatment in order to maintain disease control for 6 months in early, active axial SpA patients who were in partial remission after 28 weeks of therapy with either infliximab (IFX)+NPX or placebo+NPX.

Methods: Part I of INFAST was a double-blind, randomized controlled trial of IFX in biologic-naive patients 18–48 years of age with early, active axial SpA. Patients were randomized (2:1) to receive 28 weeks of treatment with either IV IFX 5 mg/kg (weeks 0, 2, 6, 12, 18, and 24)+NPX 1000 mg/d or IV placebo+NPX 1000 mg/d. In Part II of INFAST, patients who had achieved Assessment in Ankylosing Spondylitis (ASAS) partial remission at week 28 continued in Part II of the study with no IFX treatment. These patients were randomized in a 1:1 ratio to continue on NPX or to stop NPX until week 52. Patients from the 2 treatment arms in Part I were equally balanced over the 2 groups in Part II. The outcome explored was the proportion of subjects who maintained ASAS partial remission at week 52; detection of a treatment group difference in this small sample size would require large differences (≥40%) for statistical significance. Treatment group differences were analyzed using Fisher exact tests. MRI scores of spines and sacroiliac (SI) joints at baseline (week 28) and week 52 were used to assess inflammation. Patients with flares (BASDAI ≥30 mm [on a 0-100 mm VAS]) during 2 consecutive visits within 1–3 weeks of each other had SI and MRI and were discontinued.

Results: In preliminary results, 41 patients were randomized to NPX and 41 to no treatment in Part II of INFAST. Mean BASDAI scores (on a 0–100 VAS) at the start of follow-up were 7.1 (SD=6.6) mm and 6.2 (SD=6.9) mm in the NPX and no-treatment groups, respectively. At week 52, similar numbers of patients in the NPX group (19/40, 47.5%) and the no-treatment group (16/40, 40.0%) met the ASAS partial remission criteria, p=0.6525. Complete absence of lesions on MRI was achieved by similar numbers of patients in the NPX and no-treatment groups for combined spine and SI lesions (2.5% vs 2.5%); SI lesions alone (7.5% vs 10.0%), and spine lesions alone (50.0% vs 40.0%), all p=0.5. Few flares were experienced by patients during follow-up treatment (NPX, 1/40, 2.5% vs no treatment, 3/40, 7.5%; p=0.6153). During the follow-up period, 1 serious adverse event was reported in the no-treatment group. No deaths occurred.

Conclusions: ASAS partial remission was maintained at week 52 by 47.5% of patients who stayed on NPX therapy and 40.0% of patients in whom all treatment (IFX and NPX) was stopped.

P114

EFFICACY AND SAFETY OF ADAHILUMAB FOR THE TREATMENT OF PERIPHERAL ARTHRITIS IN SPONDYLOARTHRITIS PATIENTS WITHOUT ANKYLosing SPONDYLITIS OR PSORIATIC ARTHRITIS

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Introduction/Aim: Within the spondylarthritides (SpA) spectrum, TNF-blockade is effective for the treatment of ankylosing spondylitis (AS), psoriatic arthritis (PsA), and axial non-radiographic SpA. This study aimed to assess the efficacy and safety of adalimumab in patients with peripheral SpA not fulfilling the criteria for AS or PsA.

Methods: Forty patients with active peripheral SpA fulfilling the ESSG or Amor criteria but not the AS or PsA criteria were included. Double-blind placebo-controlled trial. Patients were treated 1:1 with adalimumab or placebo for 12 weeks, followed by an open label extension up to week 24. Safety and efficacy were assessed every 6 weeks, with as primary endpoint the patient’s global assessment of disease activity at week 12.

Results: Adalimumab, but not placebo, induced a significant improvement of the patient’s and physician’s global assessment of disease activity, swollen joint count, BASDAI, ASDAS and inflammatory parameters at week 12. A similar improvement was seen upon adalimumab treatment from week 12 to 24 in the patients originally randomized to placebo, whereas the clinical response was maintained or even augmented at week 24 in the patients originally randomized to adalimumab. These data were confirmed by direct comparison of the adalimumab and placebo group: adalimumab treated patients had significantly lower disease activities compared to placebo at week 6 and week 12. ASDAS inactive disease and BASDAI50 responses were met in 42% of adalimumab group versus 0.5% in the placebo group at week 12, and were further increased at week 24. Quality of life scores significantly improved upon adalimumab treatment. The number of adverse events was not different between the adalimumab and placebo group.

Conclusions: Adalimumab is effective and safe in SpA patients with active peripheral arthritis, also in those patients not fulfilling the AS or PsA criteria.

P115

ADALIMUMAB SIGNIFICANTLY REDUCES RECURRENT RATE OF ANTERIOR UVEITIS IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Introduction: 30-40% of AS patients suffers from acute anterior uveitis (AAU) attacks. Objective: To examine whether the use of adalimumab decreases the frequency of attacks of AAU in patients with AS, who receive this treatment due to their spinal disease activity.

Method: Consecutive AS patients, who were treated for at least 12 weeks with 40 mg of adalimumab every other week were enrolled. The number of attacks of AAU in the year before start and during adalimumab treatment was assessed by ophthalmological controls at baseline and yearly thereafter.

Results: In total 77 patients were enrolled of whom 67 (87%) were seen by the ophthalmologist at baseline and 44 (57%) during follow-up. The other data were retrieved from protocol visits to the research physician. Out of these 77 patients: 51 (66%) did not have attacks of uveitis in the year before (and during) treatment, 16 (21%) had uveitis before, but not during treatment, 10 (13%) had attacks of uveitis before and during treatment. No one developed uveitis for the first time during adalimumab treatment.

Conclusion: 34% of patients (34%) suffered from recurrent flares of uveitis in the year before start of adalimumab treatment, with a median of 2.0 uveitis attacks per year (IQR: 1.0-3.5). The median follow-up period of all patients was 1.74 years (IQR: 0.80-2.57). During follow-up, only 10 patients (13%) had attacks of uveitis with a median of 0.56 uveitis attacks per year (IQR: 0.30-0.75). This constitutes a 62% drop
in the number of patients with uveitis attacks. The number of patients with uveitis as well as the number of attacks/year dropped significantly (p<0.0001).

Conclusion: A significant and substantial reduction of recurrence rate of flares of anterior uveitis during adalimumab-treatment was found. The majority (87%) of patients remained completely free of uveitis attacks for the entire follow-up period.

P116

EUROPEAN ANKYLOSING SPONDYLITIS (AS) INFliximab Cohort (EASIC) LONG-TERM EXTENSION: EFFICACY AND SAFETY OF INFliximab OVER A TIME PERIOD OF MORE THAN 7 YEARS IN PATIENTS WITH AS


Introduction/Aim: The knowledge on long-term efficacy and safety of anti-TNF therapy in AS over longer time is limited.

Methods: 71 patients from EASIC were included in this extension, all receiving infliximab 5 mg/kg/6-8 weeks for another 96 weeks, resulting to treatment of >7 years. All adverse events (AE), serious adverse events (SAE) and drop-outs were recorded. We analyzed mean BASDAI, BASFI, patients with low BASDAI (≤3), CRP and enthesitis indexes.

Results: 64 patients (90.1%) completed 7y, while 3 discontinued (1 loss of response, 1 infection and 1 basal cell carcinoma), 1 was lost to follow-up and 3 withdrew consent. The mean BASDAI for completers was 2.4±1.7 with 42/64 (65.6%) showing low BASDAI. Three out of 6 patients with premature withdrawal showed BASDAI levels >4 at last visit. Mean CRP for completers was 4.9±5.9 mg/l at last study visit. Enthesitis scores showed no enthesis in 81% of patients. The mean BASFI of completers was 3.1±2.0. A total of 476 AE occurred in 63/71 patients (88.7%), 61 of which (96.8%) showed >1 AE, most commonly infections (35.1% of all AEs). There were 13 SAEs: 2 malignancies (1 basal cell carcinoma with discontinuation of the study, and 1 of skin melanoma where the patient decided to continue treatment because of the favourable infliximab effect). No opportunistic infections occurred. The other SAEs were considered unrelated to study drug.

Conclusion: Treatment with infliximab was efficacious and safe for AS patients over a time period of >7 years. The majority of the AEs were infections. There were no serious infections and no deaths. The two cases of skin malignancy are in line with reports from other registries.

P118

USE OF DMARDs AND ANTI-TNFs IN TREATMENT OF ANKYLOSING SPONDYLITIS AT A UNIVERSITY HOSPITAL

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Introduction: Sulfasalazine (SSA) is used widely as a second-line treatment of ankylosing spondylitis (AS) after non-steroidal anti-inflammatory drugs (NSAIDs) in Finland. Methotrexate (MTX) may be used as an alternative to SSA primarily in peripheral AS although its efficacy in AS has been questioned.

Aim: The objective of the study was to evaluate the initial use of disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) inhibitors and drug survival in AS patients at Helsinki University Central Hospital (HUCH).

Materials and Methods: From 2005 through 2009, all incident AS patients were identified in the hospital register. Index day was defined as the date of AS diagnosis. Medication and clinical data of the patients were evaluated until the end of 2010.

Results: A total of 176 patients were identified. DMARDs were prescribed to 165 patients. No one received TNF inhibitor at baseline. SSA was the first DMARD for 157 (95%) patients whereas the rest received MTX. The mean follow-up time was 3.8 years. At the baseline, Bath AS Disease Activity Index (BASDAI) was 4.1 (IQR 1.8) and decreased by ~1.6 (95% CI 2.2-1.1; p<0.001, n=46) during DMARD treatment. Twenty-eight (17%) patients became eligible for reimbursement of TNF-inhibitors and an anti-TNF was instituted. This was predicted by peripheral disease, as well as higher ESR and CRP at baseline.

Conclusion: Most incident AS patients do fairly well with DMARDs but the proportion of the patients needing anti-TNF treatment grows over time. Use of DMARDs may reduce or postpone the need for anti-TNF treatment in AS.
before start of anti-TNF-α treatment. In total, 71%, 54%, 47%, and 42% of the patients maintained on dose reduction after 6, 12, 18 and 24 months, respectively. The mean dose reduction was 37% (SD±11). Disease activity remained low (BASDAI ≤4) in 86% of the patients who continued dose reduction at 24 months. Of all 25 patients who did not continue dose reduction, 23 (92%) returned to the conventional dose regime and 2 (8%) patients stopped TNF-α blocking therapy (1 adverse event, 1 inefficacy due to antibody formation).

Conclusion: According to this observational cohort study, long-term dose reduction of TNF-α blocking agents is possible preserving low disease activity in a substantial number of AS patients.

P122
TREATMENT IN MONO-OLIGO- AND POLYARTHRITIC PA-TIENTS: A 5-YEAR STUDY ON THE SWEDISH EARLY PSORIAT-IC ARTHRITIS COHORT (SWEPSA)

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Introduction: The diverse features of psoriatic arthritis (PsA) with clinical classiﬁcation changes over time and with difﬁculties to outline treatment recommendations cause suboptimal assessment.

Patients and Methods: Patients with symptoms of PsA, referred within two years of onset were followed up according to program and classiﬁed by CASPAS.

Results: At inclusion 47% of 208 patients had mono-oligoarticular (MO) disease and 42% were classiﬁed as polyarticular (P). Nine percent had axial involvement, 2% were in remission (no tender or swollen joints, ESR and CRP within the reference range). Thirty-three percent MO were treated with DMDAR. At reclassiﬁcation 80% remained MO patients and 18% were in remission. Fifty-ﬁve % of P patients were treated with DMDAR or/and anti-TNF. At reclassiﬁcation 40% had MO disease and 8% were in remission. Signiﬁcantly more MO patients reached remission at followup compared to P patients (p=0.041). MO patients reached Minimal disease activity (MDA) more often compared to P patients at 5-year follow-up (p=0.047).

Treatment with DMDAR and/or TNF-alpha did not improve outcome MDA or remission. All P patients that reached remission were non-treated patients (p=0.006). There was a gender difference with more men reaching MDA (p=0.006) and remission (p=0.043) at 5-year follow-up, more frequent in patients before 40 years of age.

Conclusions: The effects of treatment in early PsA patients in clinical practice are not clear-cut and need to be further evaluated.

P123
EFFICACY AND SAFETY OF LOW-DOSE INFLIXIMAB IN ANKYLOSING SPONDYLITIS

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Background: Ankylosing spondylitis (AS) is a chronic disease that may result in disability and reduction in quality of life. Several anti-TNF-α agents have been shown to be effective in patients with AS. In AS Inﬁliximab (IFX) in combination with methotrexate (MTX) seems to increase the efficacy of the therapeutic response.

Objectives: The objectives of this study were to assess the efﬁcacy of low dose IFX combined with MTX in the treatment of AS that may have major cost-beneﬁt implications for the use of IFX in AS.

Methods: An open label, retrospective study including 69 patients with active AS initiating treatment with IFX at the Rheumatology Department, Sahlgrenska University Hospital, Göteborg. All patients on TNF-α therapy are registered and followed in the National Swedish Quality (SRQ) register. Primary outcome was the Bath AS disease activity indices (BASDAI).

Results: 69 patients, 72% men, median age 47.8 years (range 19-73y), BMI 26±1 and disease duration median 16y (range 14-47y), 67% with a history of peripheral arthritis, 32% with a history of iritis were studied. Low dose IFX was given, mean dose 21.2mg/2.6mg/kg, at mean 8 weeks interval. BASDAI at baseline was 4.8 (n=10) at follow up after 1 year, (n=10) 2.5, at 2 years 1.8 (n=10) at 5 years 1.8(n=13) and at 8 years 1.2. (n=5) All patients were undergoing concomitant therapy with DMDAR. Treatment survival: Of 69 patients starting therapy 10 discontinued during a median follow-up of 36months (1-104m). Reasons for the discontinuation were lack

P121
DOSE REDUCTION OF TNF-α BLOCKING AGENTS IN ANKYLOSING Spondylitis PATIENTS WITH STABLE LOW DISEASE ACTIVITY

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Introduction: Tumor necrosis factor-alpha (TNF-α) blocking agents are effective in controlling inﬂammation and improving clinical assessments in patients with ankylosing spondylitis (AS). In view of the high costs and possible side effects, our aim was to investigate whether dose reduction of TNF-α blocking agents is possible without loss of effectiveness in AS patients in daily clinical practice.

Methods: Patients included in the Groningen Leeuwarden AS (GLAS) cohort with active disease (Bath AS disease activity index (BASDAI) ≥4) before start of anti-TNF-α treatment and stable (≥6 months) low disease activity (BASDAI <4) on conventional dose regime, who started with dose reduction were studied. Data concerning medication dose, reasons for changing medication dose, and disease activity were collected after 6, 12, 18, and 24 months of dose reduction.

Results: Between November 2005 and January 2011, 49 AS patients with stable low disease activity started with dose reduction of infliximab (n=14), etanercept (n=35), or adalimumab (n=6). 88% of these patients were male, mean age was 46 years (SD±12), and mean duration of symptoms was 20 years (SD±10). Mean BASDAI was 1.8 (SD±1.1) at start of dose reduction, coming from 6.2 (SD±1.2) before start of anti-TNF-α treatment. In total, 71%, 54%, 47%, and 42% of the patients maintained on dose reduction after 6, 12, 18 and 24 months, respectively. The mean dose reduction was 37% (SD±11). Disease activity remained low (BASDAI ≤4) in 86% of the patients who continued dose reduction at 24 months. Of all 25 patients who did not continue dose reduction, 23 (92%) returned to the conventional dose regime and 2 (8%) patients stopped TNF-α blocking therapy (1 adverse event, 1 inefficacy due to antibody formation).

Conclusion: According to this observational cohort study, long-term dose reduction of TNF-α blocking agents is possible preserving low disease activity in a substantial number of AS patients.
P124

EFFECT OF LONG-TERM TNF BLOCKAGE ON LIPID PROFILE IN ANKYLOSING SPONDYLITIS PATIENTS

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Introduction: Ankylosing spondylitis (AS) patients have increased cardiovascular (CV) morbidity and mortality. Lipid profile plays an important role in development of CV disease and there are no data regarding prospective long-term evaluation of lipid profile in AS patients under TNF blockers.

Aims: To evaluate prospectively the long-term effect of anti-TNF therapy on lipid profile in AS patients and its possible association with clinical and disease parameters.

Methods and Materials: Thirty-seven consecutive AS patients, who were eligible to receive anti-TNF therapy, were prospectively enrolled. All patients were treated with TNF blockers, and they were evaluated for lipid profile, atherogenic index (AI), body mass index (BMI), waist circumference and disease parameters at baseline and at 52 and 104 weeks after treatment. Patients using statins or with LDL-cholesterol >160 mg/dL were considered at risk.

Results: Prospective evaluation of lipid profile revealed a significant increase in levels of LDL-cholesterol (98±27mg/dL vs. 109±30mg/dL vs. 117±33mg/dL, p=0.029) and a trend for an increase in total cholesterol in the same period (106±33mg/dL vs. 181±35mg/dL vs. 187±39mg/dL, p=0.057). No changes were found in the concentration of HDL-cholesterol (45±15mg/dL vs. 48±16mg/dL vs. 50±23mg/dL, p>0.05) and triglycerides (93 (75-133)mg/dL vs. 88 (72-118)mg/dL vs. 95 (76-125)mg/dL, p=0.84) or in AI (3.7±1.1 vs. 3.7±0.9 vs. 3.8±1.0, p=0.87) was observed. The proportion of patients considered at risk remained unchanged (5.3% vs. 13.5% vs. 16.2%, p=0.24). BMI (26.0±1.7kg/m2 vs. 26.4±2.6kg/m2 vs. 26.7±4.9kg/m2, p=0.76) and waist circumference (89.7±12.6cm vs. 92.1±12.2cm vs. 94.1±12.7cm, p=0.49) values remained stable throughout the study. Treatment with anti-TNF improved all disease parameters: BASDAI (p<0.001), BASFI (p<0.001), ASQoL (p=0.004), C-reactive protein (p<0.001), and erythrocyte sedimentation rate (p<0.001).

Conclusions: The novel demonstration that anti-TNF therapy has a long-term deleterious effect on LDL-cholesterol levels in AS patients, reinforces the recommendation for a close monitoring and early intervention in this modifiable cardiovascular risk factor.

P125

ANTI-TUMOR NECROSIS FACTOR AGENTS MAY PREVENT CARTILAGE LOSS OF HIP IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Aims: To determine the frequency of sarcopenia in AS patients and the effect of anti-TNF treatment in this condition.

Methods and Materials: Thirty active AS patients were assessed at baseline (BL), 6(6M), 12(12M) and 24 months(24M) after anti-TNF therapy. Patients were evaluated for clinical parameters and inflammatory markers. Physical activity remained stable during the study. Body weight and Body Mass Index(BMI) were also measured. Fat mass(FM), lean total mass(LM) and appendicular lean mass(MAS=sum of arms and legs) were analyzed by dual-energy X-ray absorptiometry(DXA). Sarcopenia was defined when the relative skeletal muscle mass index(RSMI=ASM/height(2)) was less than 5.45 kg/m2 for women and 7.26 kg/m2 for men(Baumgartner’s criteria).

Results: Sarcopenia was found in 16.6% of AS patients. There was a significant decrease in the frequency of sarcopenia with a complete reversion at 24 months (BL:16.6% vs. 6M:13.3% vs. 12M:6.6% vs. 24M:0%, p<0.001). This finding was paralleled by an increase of body weight (BL:72.65 kg vs. 6M:73.87kg vs. 12M:74.65kg vs. 24M:75.01kg, p<0.001). LM(135±43 cg vs. 12M:54.01kg vs. 24M:54.01kg, p<0.001), in particular the first in 12 months of therapy (BL vs. 12 months, p<0.05). No difference was observed in fat mass (p>0.05) and percentage of fat mass (BL:24.14% ±4.27% vs. 12M:54.08% vs. 24M:24.86%, p=0.146), BASFI (p<0.001), and ASQoL (p<0.001) improved during study period, with a significant reduction in ESR (p<0.001) and CRP levels (p<0.001) after anti-TNF therapy.

Conclusion: The novel demonstration of anti-TNF induced recovery in sarcopenia reinforces its beneficial effect in muscle mass and functional capacity in AS patients, most likely associated with a reduction of inflammation.

P126

THE EFFICACY OF TNF BLOCKADE WITH MTX THERAPY IN PATIENTS WITH TNF BLOCKADE RESISTANCE

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Introduction: This single-centre cohort study enrolled active AS patients from January 2007 to January 2012. These patients had incomplete therapeutic responses to standard therapy with non-steroidal anti-inflammatory drugs and sulfasalazine for a minimum period of 12 weeks and were treated with TNF blockade, including infliximab (IFX), adalimumab (ADL), or etanercept (ETN). We enrolled patients who showed good response after 12 weeks of TNF blockade treatment but showed decreased response during maintenance therapy. Patients with decreased response to TNF blockade, defined as increase in BASDAI score by ≥2 or 20% and in CRP by ≥2mg/L in the week of MTX, were treated with 7.5 mg/week of MTX, increased sequentially to 20 mg/week until response was observed. The primary outcome was disease activity improvement, defined as decrease in CRP and BASDAI by ≥20%.

Results: A total of 260 patients, including resistant patients, were treated with TNF blockade: 29 were IFX resistant, 13 ADL resistant, and 17 ETN resistant. In the IFX-resistant group, 26 were treated with MTX and 9 (34.6%) achieved response. In the ADL-resistant group, 10 were treated with MTX and 8 (80%) achieved response. In the ETN-resistant group, 4 were treated with MTX and 3 (75%) achieved response.

Conclusion: Combined therapy with MTX and TNF blockade was efficacious for some AS patients resistant to TNF blockade monotherapy. This finding will facilitate the decision of whether to add MTX to switch to another TNF blockade therapy for TNF blockade therapy-resistant AS patients.

P127

SARCOPENIA REVERSAL IN ANKYLOSING SPONDYLITIS (AS) UNDER ANTI-TNF THERAPY: A 24-MONTH LONGITUDINAL ANALYSIS

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Introduction: Sarcopenia is a syndrome characterized by progressive loss of skeletal muscle mass, which results in decreased muscle strength and impairment of physical and functional capacity. There are no data regarding this disorder in AS patients and the possible beneficial effect of anti-TNF therapy in this complication. Aim: To determine the frequency of sarcopenia in AS patients and the effect of anti-TNF therapy in this condition.

Methods: Thirty active AS patients were assessed at baseline (BL), 6(6M), 12(12M) and 24 months(24M) after anti-TNF therapy. Patients were evaluated for clinical parameters and inflammatory markers. Physical activity remained stable during the study. Body weight and Body Mass Index(BMI) were also measured. Fat mass(FM), lean total mass(LM) and appendicular lean mass(MAS=sum of arms and legs) were analyzed by dual-energy X-ray absorptiometry(DXA). Sarcopenia was defined when the relative skeletal muscle mass index(RSMI=ASM/height(2)) was less than 5.45 kg/m² for women and 7.26 kg/m² for men(Baumgartner’s criteria).

Results: Sarcopenia was found in 16.6% of AS patients. There was a significant decrease in the frequency of sarcopenia with a complete reversion at 24 months (BL:16.6% vs. 6M:13.3% vs. 12M:6.6% vs. 24M:0%, p<0.001). This finding was paralleled by an increase of body weight (BL:72.65 kg vs. 6M:73.87kg vs. 12M:74.65kg vs. 24M:75.01kg, p<0.001). LM(135±43 cg vs. 12M:54.01kg vs. 24M:54.01kg, p<0.001), in particular the first in 12 months of therapy (BL vs. 12 months, p<0.05). No difference was observed in fat mass (p>0.05) and percentage of fat mass (BL:24.14% ±4.27% vs. 12M:54.08% vs. 24M:24.86%, p=0.146), BASFI (p<0.001), and ASQoL (p<0.001) improved during study period, with a significant reduction in ESR (p<0.001) and CRP levels (p<0.001) after anti-TNF therapy.

Conclusion: The novel demonstration of anti-TNF induced recovery in sarcopenia reinforces its beneficial effect in muscle mass and functional capacity in AS patients, most likely associated with a reduction of inflammation.
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TAPERING INFlixIMAB IN ANKYLOSING SPONDYLITIS: CAN WE REDUCE COSTS?

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Introduction: The approved dose for infliximab (IFX) in the treatment of ankylosing spondylitis (AS) is 5mg/kg body weight every 6 weeks. Several studies have shown the 3mg/kg dose to be effective in a subgroup of AS patients but there is few published evidence regarding other dose-reduction regimens, namely adjusting the interval between doses and individualized dose adjustment. We analyzed AS patients disease activity upon increasing IFX administrations intervals on an individual basis.

Methods: The Rheumatic Disease Portuguese Register was used to select all patients diagnosed with AS, under IFX therapy for ≥4 months, followed at Santa Maria Hospital. All patients received IFX 5mg/kg at 0-2-6 weeks and thereafter at variable intervals, between 6 and 11 weeks, on an individual basis, determined by clinical judgement. Response to treatment was assessed using BASDAI and ASDAS. Clinical remission was defined as an ASDAS<1.3 for 4 months.

Results: 50 patients were followed for a mean time of 57±35 months. 11 patients (22%) were maintained on IFX every 6 weeks, 12 (24%) increased the interval between doses immediately after week 6 and 23 (46%) increased interval between doses after a mean time receiving IFX of 18.2±11.1 months. BASDAI improvement (meanSD) between starting IFX therapy and the last visit was of 3.7±2.3; 56% had met the BASDAI50 criteria. 65% of patients had achieved a BASDAI50 response at the time of physician decision to increase administration intervals. 21 patients (42%) achieved remission, 21.5±2.8 months after starting IFX. Regarding these patients, 16 (76%) showed persistent remission, 5 (24%) had recurrence of activity (ASDAS≥1.3), on average 12.9 months after remission; at the last visit 19 (90%) had ASDAS<1.3.

Conclusion: This study confirms that increasing IFX administration intervals can be performed in clinical practice in a subgroup of patient without worsening of disease activity. A high percentage of patients achieved remission (42%) and maintained it through follow-up (32%).

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ANTI-TNF THERAPY SLOWS RADIOGRAPHIC PROGRESSION OF ANKYLOSING SPONDYLITIS AND OPPOSES THE EFFECTS OF SMOKING AND INFLAMMATION

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Introduction: The influence of anti-TNF therapy on radiographic progression in ankylosing spondylitis (AS) is not well established. We studied this effect on radiographic progression in AS patients.

Methods: Patients with AS satisfying the modified New York criteria were enrolled from Canada (N=151) and USA (N=150). Patients with bamboo spine at baseline were excluded. Radiographs were done at an interval of at least 1.5 years and read by one reader for all US centers and by two readers for Toronto. Patients were followed once (Toronto) or twice (USA) annually. Time-averaged BASDAI, ESR and CRP, NSAID use or NSAID index was not significant in the univariate analysis. In multivariate analysis, after adjusting for significant factors in the univariate analysis, the following variables remained significant: baseline CRP (β=1.02; p=0.012), baseline mSASSS (β=1.09; p=0.010) and use of anti-TNF treatment (β=4.2; p=1x10^-6).

Conclusions: Baseline and persistent Inflammation is associated with radiographic progression in AS. Anti-TNF therapy can slow the rate of radiographic progression in AS.
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